Indo Global Journal of Pharmaceutical Sciences, 2020; 10(4): 32-38

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

Improvement in Drug Release and Pharmacokinetic Parameters of Ketoprofen Crystals

Pooja D. Vaghela [1*], H.M. Tank [2], N.U. Patel [3], P.I. Shah [1], M.L. Rathod [4]

[1] *Shantilal Shah Pharmacy College, M. K. Bhavnagar University, Bhavnagar -364002, Gujarat, India*

[2] *Aatmiya Institute, Rajkot, India*

[3] *Shri B. M. Shah College of Pharmacy, Modasa, India*

[4] *B. K. Mody Government Pharmacy College, Rajkot*, India

Address for Correspondence: Pooja D. Vaghela, poojavaghela786@gmail.com

Received: 08.02.2019
Accepted: 13.12.2019
Published: 15.12.2020

Keywords
Crystallization; Pharmacokinetic parameters; Bioavailability; Cmax; Tmax.

ABSTRACT: Purpose: The aim of present work was to improve the in-vitro drug release from crystal formulation with the improvement in pharmacokinetic parameters like Cmax, Tmax, and AUC of Ketoprofen by crystal engineering approach. Methods: Ketoprofen crystals were prepared by conventional solvent evaporation process in presence of saccharin sodium excipient at room temperature. Control batch was also prepared by the same technique with devoid of excipient. The prepared crystals were subjected for in-vitro and in-vivo study and the results obtained were compared with the pure drug. Results: In-vitro dissolution study shows the improvement in 2.05 fold drug release rate from Ketoprofen treated crystals compared to the pure drug. In-vivo analysis was carried out by using albino wistar rats which shows the improvement in 2.13 fold higher plasma concentration compared to the pure drug. The results revealed that one group of rats treated with pure drug i.e., Ketoprofen suspension (STANDARD) while the other group of rats treated with Ketoprofen loaded crystals (TEST), the plasma concentration-time profile depicted Cmax of 27900.37 ng/mL and 46155.29 ng/mL while Tmax of 120 minutes and 30 minutes, and AUC found was 221146.22 ng*h/mL and 471504.04 ng*h/mL respectively. Plasma concentration-time profile represented that Ketoprofen loaded crystals (TEST) gave higher plasma concentration (2.13 fold) compared to Ketoprofen pure drug (STANDARD). Conclusions: The crystal engineering approach can be used to improve the poor aqueous solubility and ultimately used to improve plasma concentration of BCS Class-II drugs.

Cite this article as: Vaghela, P.D.; Tank, H.M.; Patel, N.U.; Shah, P.I.; Rathod, M.L. Improvement in drug release and pharmacokinetic parameters of ketoprofen crystals. Indo Global J. Pharm. Sci., 2020; 10(4): 32-38.
DOI: http://doi.org/10.35652/IGJPS.2020.10406 .

INTRODUCTION

Ketoprofen is having poor water solubility, BCS class II drug, and is of propionic acid derivative drug which is used as a potent non-steroidal anti-inflammatory drug (NSAID) and is used for the symptomatic treatment of osteoarthritis, spondylitis, rheumatoid arthritis, and is widely used clinically as antipyretic, and anti-inflammatory agent. On the basis of powder rheology, it is classified as a powder with poor flow property and compressibility [1-5] which is not processed by directly compressible technique. Moreover, Ketoprofen is a BCS Class II drug which has poor aqueous solubility [6, 7] and high permeability with analgesic activity which is processed by crystal engineering approach and prepared Ketoprofen loaded crystals shows improvement in the aqueous solubility [8], *in-vitro* drug release rate and ultimately it improves the pharmacokinetic parameters of Ketoprofen.

Ketoprofen metabolized in the liver by way of conjugation with CYP3A4 and CYP2C9, glucuronic acid, reduction of its keto group and hydroxylation of the benzoyl ring system [9-12]. Primarily, Ketoprofen is used as an anti-inflammatory, antipyretic and analgesic drug which decreases the prostaglandin precursor synthesis which act by reversibly inhibiting both cyclooxygenase enzymes i.e., COX-1 and COX-2 [11, 13]. Ketoprofen is well absorbed after oral

administration and peak plasma level of the conventional capsules can be attained within 0.5–2 hours or 6–7 hours upon administration of extended release capsules [14-21]. The peak plasma level of Ketoprofen delayed by food material [22]. Ketoprofen is rapidly and extensively metabolized in the liver and mainly excreted in urine. Half-life of conventional capsules is about 2-4 hours and extended release capsules is about 4-5 hours [22].

Ketoprofen is mainly used as an anti-inflammatory drug in arthritis, toothache and in the skeletal muscle pain in form of topical patches [23-25]. Ketoprofen ointment, spray, cream, liquid or gel along with other appropriate agents may use in the treatment of nerve pain such as neuralgia, raticulopathy, inflammatory conditions, sciatica etc. as an anti-inflammatory agent in the treatment of pain.

MATERIALS AND METHODS

1. Materials

Ketoprofen (KETO) was gifted by Emcure Pharmaceuticals Limited, Pune. Potassium dihydrogen phosphate (KH_2PO_4) and Disodium hydrogen orthophsophate dihydrate (Na_2HPO_4) were purchased from SDFCL, Mumbai. Sodium Hydroxide (NaOH) and Sodium acetate trihydrate were procured from Rankem, New Delhi, India. Saccharin sodium dihydrate (SAC-Na) was gifted by Pure Chem. Pvt. Ltd., Ankleshwar, Gujarat. All other solvents, excipients and chemicals used were of analytical and HPLC grade (Merck Pvt. Ltd., Mumbai, India).

2. Crystal preparation by conventional solvent evaporation technique

Ketoprofen loaded crystals were prepared by solvent evaporation technique using Saccharin sodium dihydrate excipient in molar proportion of (1M:1M) which formed hydrogen bonding with Ketoprofen. This bond lead to improve physicochemical properties of Ketoprofen like aqueous solubility [8], *in-vitro* dissolution rate and ultimately improve pharmacokinetic parameters like C_{max}, T_{max} and AUC by *in-vivo* study which was investigated and presented in this work. A batch of control crystals was also formulated without adding excipient by keeping same other experimental parameters [26].

3. Drug release study of Ketoprofen crystals, control batch and pure drug

As per IP-X, *In-vitro* dissolution measurements were carried out in USP dissolution test apparatus (Electrolab Dissolution Tester TDT-06P, USP). The dissolution profile of Ketoprofen pure drug, control batch and Ketoprofen loaded crystals were studied in 900 mL of Phosphate buffer pH 7.5. 100 mg Ketoprofen pure drug and its control batch were filled in capsule separately while in case of drug-loaded crystals, 100 mg equivalent to Ketoprofen drug was filled and placed in a dissolution flask containing 900 mL of the dissolution medium, thermostated at 37 ± 0.5 °C, with paddle (USP Type II) with rotation speed of 50 RPM for one hour.

After each time interval i.e., 5, 10, 15, 20, 30, 40, 50 and 60 minutes, the samples (5 mL) were withdrawn and replaced immediately with fresh dissolution medium. The samples were filtered and one milliliter of the filtrate was diluted with respective buffer solution till the absorbance was measured in the range of 0.2 - 0.8. All the samples were assayed similarly by measuring the absorbance spectrophotometrically at 260 nm wavelength for dissolved drug. The dissolution experiments were conducted in triplicate and the mean of the absorbance was calculated. After one hour of dissolution, the amount (%) of the Ketoprofen drug dissolved were calculated graphically and used as comparison parameter in dissolution studies.

4. Pharmacokinetic study of Ketoprofen crystals compared with pure drug

Wistar albino rats (weighing approximately 210 ± 30 g) of either sex were used for the pharmacokinetic study of Ketoprofen pure drug and Ketoprofen loaded crystals. The animals were maintained in temperature and humidity controlled room with a 12:12 h light:dark cycle and were supplied with food and water *ad libitum*. The animal requirement for pharmacokinetic study of Ketoprofen was approved by the Institutional Animal Ethics Committee (IAEC) with protocol number **IAEC/DPS/SU/1522** and all experiments were conducted as per the norms of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India [6, 7].

The overnight fasted rats (~12 h; n=4) with free access to water were used for the experiment of Ketoprofen pure drug and Ketoprofen loaded crystals. Two groups of rats were used among which one group was administered orally with aqueous suspension of Ketoprofen pure drug (STANDARD group) and another group was administered with Ketoprofen loaded crystals (TEST group) [27-30].

Samples of the Ketoprofen pure drug (9 mg/kg) (obtained by converting human dose to rat dose [30, 31]) and Ketoprofen loaded crystals (9 mg/kg equivalent to Ketoprofen) were accurately weighed and separately dispersed into distilled water (3 mL) by mixing homogeneously for 30 s prior to dosing. Each formulation was administered separately to rats by oral gavage using an animal feeding needle.

4.1 Collection of blood samples

Under ether anesthesia, blood samples (0.5 mL) were collected via the retro-orbital plexus at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 6, 12 and 24 hours, after oral administration, into polypropylene tubes containing K3EDTA solution as anticoagulant tubes. The plasma was harvested by centrifuging the blood at 15000 rpm for 10 min at 4 °C temperature using a cooling centrifuge (REMI, Mumbai, India) and stored frozen in Deep freeze (Remi Quick Freezer, Mumbai, India) at -80 ± 10 °C until analysis. Both group animals were allowed to feed 2 h post-dose.

An aliquot of 300 µL of thawed plasma samples was processed as described in the following sample preparation sections.

4.2 Preparation of calibration curve of Ketoprofen in rat plasma (Spiked CC Standards)

Drug free rat plasma having K3EDTA as an anticoagulant was procured from Department of Pharmaceutical Sciences, Saurashtra University, Rajkot. CC standards were prepared by spiking the respective CC spiking solutions in drug free K3EDTA rat plasma as described in **Table 1**.

4.3 Quality control (QC) spiking solutions

QC spiking solutions were prepared in Methanol using Drug Stock Solution (2 mg/mL) by serial dilution as described in **Table 2**.

4.4 Equipment conditions

4.4.1 Chromatographic conditions

The concentration of Ketoprofen in rat plasma of both groups were determined by HPLC (LC20AD, Shimadzu Corporation, Japan) analysis consisted of binary gradient system with Photon Diode Array (PDA) Detector and Lab Solution Software 5.72 B (Shimadzu Corporation, Japan). HPLC system equipped with binary pump (LC-20AD) along with an auto sampler (SIL-HTC) was used to inject 10 µL plasma of the samples, processed as described in the extraction procedure section**,** onto a chromatographic column Gemini C 18, 150 mm x 4.6 mm, 5 µm. The chromatographic conditions for Ketoprofen is described in **Table 3**.

Table 1. Spiked CC standards in rat plasma for Ketoprofen

Spiking Solution ID	Spiking Solution Conc. (µg/mL)	Spiking Volume (mL)	Plasma Volume (mL)	Total Volume (mL)	Spiked Conc. (µg/mL)	STD ID
Methanol	0	0.5	9.5	10	0	STD BL
SS STD1	1000	0.5	9.5	10	50	STD 1
SS STD2	500	0.5	9.5	10	25	STD 2
SS STD3	250	0.5	9.5	10	12.5	STD 3
SS STD4	100	0.5	9.5	10	5	STD 4
SS STD5	50	0.5	9.5	10	2.5	STD 5
SS STD6	30	0.5	9.5	10	1.5	STD 6
SS STD7	16	0.5	9.5	10	0.8	STD 7
SS STD8	8	0.5	9.5	10	0.4	STD8
SS STD9	4	0.5	9.5	10	0.2	STD9
SS STD10	2	0.5	9.5	10	0.1	STD10

Table 2. Quality control (QC) spiking solutions for Ketoprofen

Stock Dil. Conc. (µg/mL)	Volume Taken (mL)	Volume of Methanol (mL)	Total Volume (mL)	Spiking Solution Conc. (µg/mL)	Spiking Solution ID
2000	2.25	2.75	5	900	SS HQC
900	2	4	6	300	SS MQC
300	0.4	4.6	5	24	SS LQC

Data from the plasma samples of both groups were used to plot curves for the estimation of concentration of Ketoprofen in plasma with time and also used for the comparison of pharmacokinetic parameters of Ketoprofen loaded crystals (Test) with Ketoprofen pure drug (Standard).

Table 3. Chromatographic conditions for Ketoprofen

Parameters	Used
Column	Gemini C 18, 150 mm x 4.6 mm, 5 µm
Mobile Phase	Formic acid in water, 0.1 %v/v : Methanol, 35 : 65 %v/v
Flow rate	1.00 mL/min,
Column oven temperature	40 ± 0.3 °C
Auto sampler temperature	15 ± 3 °C
Volume of injection	10.0 µL
Detector	PDA detector
Retention time	Analyte at about 5.13 minutes
	ISTD at about 3.50 minutes
Run time	8.0 minutes

4.5 Extraction procedure

4.5.1 Procedure for extracted sample preparation

Note: 500 µL of respective spiking solution was spiked into tube containing 9500 µL of rat plasma & vortex to mix.

Step 1. Retrieve the required number of CC standards and QC samples from the deep freezer, thaw them at R.T. and vortex the tubes to mix. Transfer 0.3 mL of sample into pre-labelled tube.

Step 2. Add 50 µL of ISTD (Internal Standard) dilution to all the samples except STD Blank and vortex for about 15 seconds.

Step 3. Add 50 µL of 0.1 N Hydrochloric acid in water solution to all the samples and vortex for about 15 seconds.

Step 4. Add 1.2 mL of Ethyl acetate, cap the tubes and vortex all the samples on cyclo mixer, for 10 minutes.

Step 5. Extracted samples were centrifuged at 10000 RPM, at 10 ± 2 °C for 10 minutes.

Step 6. 1.0 mL of supernatant was transferred into pre-labelled tubes and evaporated to dryness under vacuum by using an vacuum oven set at 40 ± 5 ^{o}C.

Step 7. After drying, samples were reconstituted with 100 µL of reconstitution solution and vortexed for about 30 seconds.

Step 8. Reconstituted samples were transfer into pre-labeled auto sampler vials, arrange them in the auto sampler and inject by using HPLC-PDA.

4.5.2 Aqueous sample preparation

1. Take 350 µL of reconstitution solution in pre-labelled tubes.
2. Add 500 µL of ISTD dilution, vortex to mix.
3. Add 150 µL of respective spiking solution and vortex to mix.
4. Appropriate volume of samples was transfer into pre-labelled auto sampler vials, and injected by HPLC-PDA.

4.5.3 Post spiked sample preparation for recovery experiment for drug and ISTD

Step 1. Retrieve the required number of STD BL from the deep freezer, thaw them at R.T. and vortex the tubes to mix. Transfer 0.3 mL of sample into pre-labelled tube.

Step 2. Add 50 µL of Methanol to all the samples, vortex for about 15 seconds.

Step 3. Add 50 µL of 0.1 N Hydrochloric acid in water solution to all the samples and vortex for about 15 seconds.

Step 4. Add 1.2 mL of Ethyl acetate to all samples and vortex for about 15 seconds.

Step 5. Centrifuge the samples at 10000 RPM, at 10 ± 2 °C for 10 minutes.

Step 6. 1.0 mL of supernatant was transferred into pre-labelled tubes and evaporated to dryness under vacuum by using the vacuum oven set at 40 ± 5 ^{o}C.

Step 7. After drying, samples were reconstituted with 100 µL of respective aqueous solution (Vial) and vortexed for about 30 seconds.

Step 8. Transfer samples into pre-labeled auto sampler vials, arrange them in the auto sampler and inject by using HPLC-PDA.

5. Data processing

The chromatograms were acquired by using Lab Solution Software 5.72 B supplied by Shimadzu. The calibration curve was plotted as the peak area ratio (Drug/ISTD) on Y-axis Vs the nominal concentration of Drug on the X-axis. The

concentrations of the unknown samples were calculated by using linear regression equation with $1/C^2$ weighting factor.

6. Pharmacokinetic parameters

Pharmacokinetic parameters C_{max} and T_{max} were calculated using plasma concentration versus time profile. The area under the plasma concentration versus time curve from zero time to the last experiment point, ($AUC_{0\rightarrow 24h}$) was calculated by trapezoidal method.

6.1 Trapezoidal method

The plot of plasma concentration time profile is divided into geometric figures whose area can be determined individually using appropriate geometric formula for each figure. The area under the curve of plasma concentration time plot was obtained by adding the area of each segment represented by the geometric figure. This plot resulted into one triangle and remaining trapezoids [32]. The following relationship was used to calculate each geometric figure.

AUC = $[(0.5)\ (c_1 + c_2)\ (t_2 - t_1) + \ldots\ldots n]$

Area of triangle = (0.5) (height) (base)

Area of trapezoid = (0.5) (sum of two parallel sides) ($base_2$ - $base_1$)

AUC = Area of triangle + Total area of trapezoids

RESULTS AND DISCUSSION

In-Vitro drug release study

In-Vitro drug release profile of Ketoprofen pure drug, its control batch and treated crystals were studied and results obtained are illustrated in the following Figure. *In-vitro* dissolution profile (**Figure 1**) depicted that treated crystal formulation with 1:1 molar proportion showed greater drug release (57.88%) with 2.05 fold while in case of 1:2 molar ratio of KETO:SAC-Na (52.54%) with 1.86 fold drug release compared to Ketoprofen pure drug within one hour. Results also revealed that the treated crystals showed drastic increase in dissolution rate compared to control batch (48.77%) as well as pure drug (28.27%) within one hour.

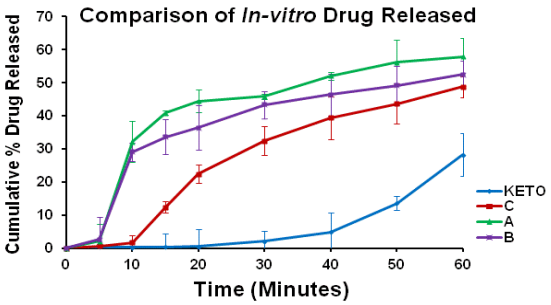

Figure 1. Comparison Of In-Vitro Drug Release Profile In Phosphate Buffer pH 7.5 At 37 °C ± 0.5 °C. Ketoprofen Drug (KETO), Control Batch (C), Treated Crystals Of KETO:SAC-Na [1M:1M] (A) And Treated Crystals Of KETO:SAC-Na [1M:2M] (B)

From the above results, it was concluded that the solubility and dissolution rate of treated crystals with molar ratio 1:1 of KETO:SAC-Na was better than pure drug, control batch and other molar ratio 1:2 of KETO:SAC-Na. Therefore, molar ratio of 1:1 was selected as optimized ratio for the *in-vivo* pharmacokinetic study.

In-Vivo pharmacokinetic study

Preparation of calibration curve of Ketoprofen with internal standard Carbamazepine (CBZ) in rat plasma (Spiked CC Standards)

Peak of Ketoprofen with internal standard Carbamazepine in rat plasma by HPLC method is illustrated in **Figure 2** and calibration curve of Ibuprofen in rat plasma by HPLC method is illustrated in **Figure 3**.

Comparison of mean plasma concentration - time profile of Ketoprofen drug with its treated crystals in rat plasma

In-vivo absorption study was carried out to assess the solubility and dissolution enhancement of Ketoprofen in treated crystal formulation. Enhancement of *In-vitro* dissolution of drug from treated crystals could increase the GI absorption of drug after oral administration.

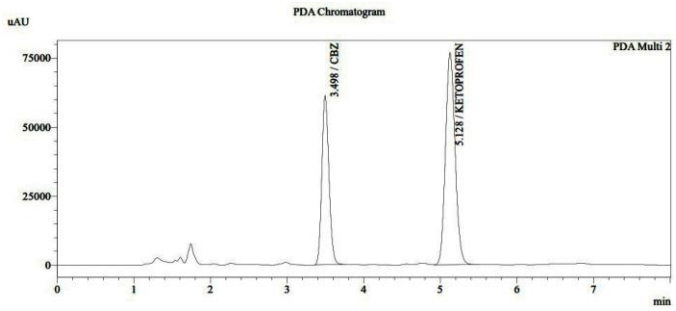

Figure 2 Peak of Ketoprofen with internal standard carbamazepine (CBZ) in rat plasma by HPLC method

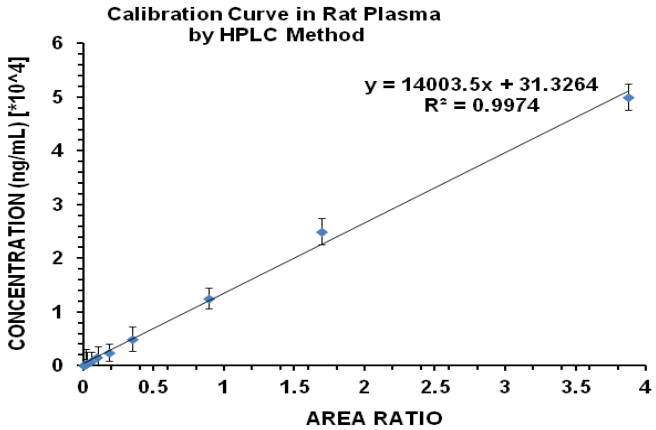

Figure 3 Calibration curve of Ketoprofen in rat plasma by HPLC method

The plasma concentration - time profiles of Ketoprofen in albino rats (Wistar strain) following oral administration of suspension of Ketoprofen pure drug (**STANDARD**) and treated crystal formulation (**TEST**) are revealed and depicted in **Figure 4**.

Table 4. Comparison of pharmacokinetic parameters of pure Ketoprofen drug (STANDARD) with treated crystals (TEST)

Pharmacokinetic Parameters	Ketoprofen Pure Drug (STANDARD)	Treated Crystals (TEST)
C_{max} (ng/mL) ± SD*	27900.37 ng/mL ± 3263.74	46155.29 ng/mL ± 3345.93
T_{max} (h) ± SD*	2 h ± 0.05	0.5 h ± 0.02
$AUC_{0\rightarrow24}$ (ng*h/mL) ± SD*	221146.22 ng*h/mL ± 97589.60	471504.04 ng*h/mL ± 76540.95
* Results are expressed as mean ± SD (n = 4)		
[a] Significantly different from Pure drug, P < 0.05		

By examining the results obtained from the above individual analysis, it was revealed that the rats treated with pure drug i.e., Ketoprofen suspension (**STANDARD**) and Ketoprofen loaded crystals (**TEST**), the plasma concentration-time profile observed C_{max} of 27900.37 ng/mL and 46155.29 ng/mL while T_{max} of 120 minutes and 30 minutes, respectively as shown in **Figure 4**.

Plasma concentration-time profile represented that Ketoprofen loaded crystals (1M:1M) (**TEST**) gave higher plasma concentration (2.13 fold) compared to Ketoprofen pure drug (**STANDARD**). It was observed that Ketoprofen loaded crystals increased the rate of dissolution by way of hydrogen bonding with Saccharin sodium excipient. Hence, there was a drastic increment in the absorption of Ketoprofen from its crystal formulation which also enhanced the pharmacokinetic parameters and bioavailability of the drug.

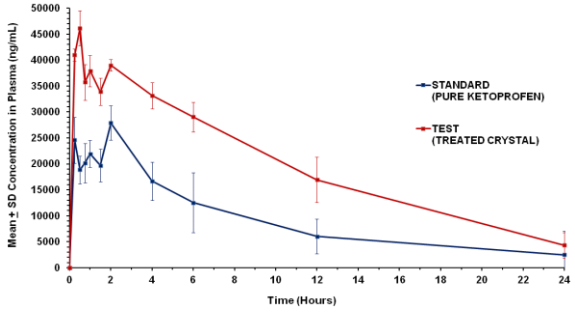

Figure 4 Comparison of mean plasma concentration - time profile following oral dose of pure Ketoprofen (STANDARD) and Ketoprofen loaded crystal (TEST) in rat plasma

Consequently, the pharmacokinetic parameters illustrated in **Table 4** explained that Ketoprofen loaded crystal formulation exhibited better dissolution of drug in stomach. Hence, better absorption was achieved compared to pure drug. As shown in **Table 4**, T_{max} for pure drug was achieved in 2 hours whereas for treated crystals, it was only 0.5 hour. The plasma drug concentration of treated crystals was 46155.29 ng/mL (TEST) which was again much higher compared to the plasma drug concentration of pure drug (STANDARD) i.e., 27900.37 ng/mL.

CONCLUSION

The aim of present work was to study the improvement in the *in-vitro* drug release and pharmacokinetic parameters of Ketoprofen treated crystals compared to the pure/plain drug as in the previous study it was found the improvement in aqueous solubility, drug release rate and mechanical properties which lead to the improvement in phsicochemical, mechanical and pharmacotechnical parameters of Ketoprofen, BCS Class II drug having poor flow property. In the present study, it was found that the Ketoprofen loaded crystals could drastically increase the dissolution rate and ultimately improve the pharmacokinetic parameters like C_{max}, T_{max} and AUC compared to the pure Ketoprofen drug.

ACKNOWLEDGEMENT

The present research work is of Ph. D. enrolled at R. K. University, Rajkot. The authors greatly acknowledge Emcure Pharmaceuticals Limited, Pune, India and Pure Chem. Pvt. Ltd., Ankleshwar, Gujarat, India for providing the gift samples of Ketoprofen and Saccharin sodium dihydrate, respectively. Authors are also extend the sincere gratitude to the Principal, B. K. Mody Government Pharmacy College, Rajkot and the HOD, Department of Pharmaceutical Sciences, Rajkot for assistance in the present research work by providing various instrumental facilities. This work was supported and funded by the Gujarat Council on Science and Technology (GUJCOST), Gandhinagar (Ref. No. GUJCOST/MRP/2014-15/2565, Dated 30/03/2015) and hence authors are very much grateful for their kind financial assistance in the present study.

DATA AVAILABILITY

Not declared.

CONFLICTS OF INTEREST

The authors declare no conflict of interest in this research article.

FUNDING SOURCE

This work was supported and funded by the Gujarat Council on Science and Technology (GUJCOST), Gandhinagar (Ref. No. GUJCOST/MRP/2014-15/2565, Dated 30/03/2015) and hence authors are very much grateful for their kind financial assistance in the present study.

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