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**Original Research Article**

# Physical characterization and kinetic modelling of matrix tablets of ketorolac tromethamol formulated with polymers and waxes

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## Abstract

***Purpose:*** *To design controlled release ketorolac tromethamol (KT) matrix tablets for increased drug bioavailability.*
***Methods:*** *Waxes (Compritol® ATO 888, Precirol® ATO 5 and stearic acid - SA) and polymers (hydroxypropyl methylcellulose - HPMC and xanthan gum - XG) were used in the preparation of the matrix tablets at various excipient concentrations for controlled drug delivery. The physical properties of the formulations were determined. Drug release profiles from the tablets were obtained and their drug release mechanisms were characterized by kinetic modeling. Analytical quantification method of KT in dissolution media was also validated by certain performance criteria.*
***Results:*** *KT matrix tablets prepared individually with Compritol and HPMC at 30 and 40 % concentrations, respectively, displayed the best tablet compression properties. The tablets prepared with HPMC and XG displayed slower drug release profiles compared to the tablets prepared with waxes in general ($p < 0.05$). KT release increased with increase in pH since it is a weak acid ($p < 0.05$). Statistically insignificant difference was observed among all the tablets prepared with HPMC and XG in water ($p > 0.05$). However, drug release from the tablets containing 40 % XG was faster than tablets prepared with HPMC (30 and 40 %) and XG (30 %) at pH 7.2 ($p < 0.05$). Drug release mechanisms from the tablets prepared with wax and polymers were non-Fickian, indicating coupled diffusion/erosion and diffusion/polymer relaxation, respectively.*
***Conclusion:*** *KT matrix tablets have been successfully formulated by direct compression method. The findings demonstrate that both the desired physical characteristics and drug release profiles were obtained for matrix tablets prepared with HPMC.*

***Keywords:*** *Ketorolac tromethamol, Controlled release, Matrix tablets, Oral drug delivery, Waxes, Polymers*

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## INTRODUCTION

Ketorolac tromethamol (KT) [(±) - 5-benzoyl - 2, 3 - dihydro - 1H – pyrrolizine - 1 -carboxylic acid compound with 2 - amino - 2 - (hydroxymethyl) - 1, 3 – propanediol (1:1)] is a non-steroidal anti-inflammatory drug (NSAID) of heterocyclic acetic acid derivatives which has a pKa of 3.54 [1,2]. It is used for short-term management of moderately severe acute and/or postoperative pain to reduce postoperative narcotic requirements. It is rapidly and completely absorbed in gastrointestinal tract. Its terminal half-life has been reported to be in the range of 5.5 h for healthy subjects. Peak plasma concentration occurs averagely 35 min after

administration of single dose. Its recommended initial dose is 10 mg followed by 10 - 30 mg every 4 - 6 h. It is prescribed for not more than 5 days for adults and as a single dose for children. Because of the risk of possible serious side effects, it is not suitable for long-term therapy [3,4] related to gastrointestinal system (ulceration, bleeding and/or perforation of the stomach or intestines), vascular (cerebrovascular bleeding) and cardiovascular systems (cardiovascular thrombosis, myocardial infarction and stroke), urinary system (renal impairment).

The undesirable side effects of KT can be minimized if it is introduced in a dosage form that provides controlled drug delivery after oral administration. Matrix tablets are suitable dosage forms in this regard. When they provide sustained drug release in the gastrointestinal track, risk of systemic side effects of drugs can be minimized by administering lower daily dose to the patients. Matrix tablets also relatively easy and cost-effective to produce with high reproducibility, unlike conventional tablets for rapid drug release [5,6].

The aim of this study was to design matrix tablets of KT for sustained drug release. Thus, maintaining drug in the systemic circulation for a longer time period, using a low dose may decrease the risk of side effects of KT, thus enhancing patient compliance to therapy.

## EXPERIMENTAL

### Materials

Ketorolac tromethamol was provided from Dr. Reddy's Laboratories Ltd. in India. Precirol® ATO 5 and Compritol® 888 ATO were obtained from Gattefossé in France. Stearic acid, xanthan gum and polyvinylpyrollidone K-90 were purchased from Cognis (Germany), CP Kelco (USA) and BASF (Germany), respectively. Methocel® K15 Premium EP was kindly provided from Colorcon (England). Avicel® PH-102 and magnesium stearate were obtained from Select-chemie AG (Switzerland) and Prever (Italy), respectively.

### Preparation of matrix tablets

Placebo and KT tablets were prepared by direct compression method. KT tablets were formulated containing 40 mg KT in 180 mg total tablet weight (Table 1). Tablets were compressed by using a biconvex punch 8.0 mm in diameter on a single punch tabletting machine (Korsch EK/O, Germany) under 6895 kp compression force.

### Physical characterization of matrix tablets

Carr's indexes (CI) and Hausner ratios (HR) of powder mixtures were determined before compression of placebo and KT matrix tablets [7,8].

**Table 1:** Composition (%) of placebo and ketorolac tromethamol (KT) matrix tablets

| Formulation | | Ingredient (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | KT | Avicel | Compritol | Precirol | SA | HPMC | XG | PVP-K 90 | Aerosil | Magnesium stearate |
| Placebo tablets | PCo-30 | - | 63.20 | 30 | - | - | - | - | 5 | 0.8 | 1 |
| | PCo-40 | - | 53.20 | 40 | - | - | - | - | 5 | 0.8 | 1 |
| | PPr-30 | - | 63.20 | - | 30 | - | - | - | 5 | 0.8 | 1 |
| | PPr-40 | - | 53.20 | - | 40 | - | - | - | 5 | 0.8 | 1 |
| | PSA-30 | - | 63.20 | - | - | 30 | - | - | 5 | 0.8 | 1 |
| | PSA-40 | - | 53.20 | - | - | 40 | - | - | 5 | 0.8 | 1 |
| | PHPMC-30 | - | 63.20 | - | - | - | 30 | - | 5 | 0.8 | 1 |
| | PHPMC-40 | - | 53.20 | - | - | - | 40 | - | 5 | 0.8 | 1 |
| | PXG-30 | - | 63.20 | - | - | - | - | 30 | 5 | 0.8 | 1 |
| | PXG-40 | - | 53.20 | - | - | - | - | 40 | 5 | 0.8 | 1 |
| KT tablets | Co-30 | 22.22 | 40.98 | 30 | - | - | - | - | 5 | 0.8 | 1 |
| | Co-40 | 22.22 | 30.98 | 40 | - | - | - | - | 5 | 0.8 | 1 |
| | Pr-30 | 22.22 | 40.98 | - | 30 | - | - | - | 5 | 0.8 | 1 |
| | Pr-40 | 22.22 | 30.98 | - | 40 | - | - | - | 5 | 0.8 | 1 |
| | SA-30 | 22.22 | 40.98 | - | - | 30 | - | - | 5 | 0.8 | 1 |
| | SA-40 | 22.22 | 30.98 | - | - | 40 | - | - | 5 | 0.8 | 1 |
| | HPMC-30 | 22.22 | 40.98 | - | - | - | 30 | - | 5 | 0.8 | 1 |
| | HPMC-40 | 22.22 | 30.98 | - | - | - | 40 | - | 5 | 0.8 | 1 |
| | XG-30 | 22.22 | 40.98 | - | - | - | - | 30 | 5 | 0.8 | 1 |
| | XG-40 | 22.22 | 30.98 | - | - | - | - | 40 | 5 | 0.8 | 1 |

***Note:*** Each formulation also contained PVP K90 (5 %), Aerosil (0.8 %) and magnesium stearate (1 %)

Bulk volume of 10 g of powder in a 25 mL measuring cylinder was recorded and the powder was then tapped 1250 times in a packed density apparatus (Erweka SVM 202, Germany) to determine packed volume. CI and HR were calculated via bulk and packed densities [9].

Physical characterization of tablets was tested in order to determine weight variation, tablet diameter and thickness, hardness, percent friability, disintegration time [10,11]. Variations in tablet weights were determined on 20 tablets using a balance (Denver Instrument). Friability was determined by using 20 tablets in an Erweka TAR 220 friability tester (Germany) for 4 min at 25 rpm. Disintegration time of 6 tablets of each formulation was determined using an Erweka ZT 320 disintegrator (Germany) according to USP 32. Diameter, thickness and hardness of 10 tablets of each formulation was tested with an Erweka TBH 525 hardness tester (Germany). Tensile strength was obtained from the fracture of tablets by diametral compression [10,12].

**Validation of analytical method for quantification of ketorolac tromethamol**

The analytical method for quantification of KT in distilled water, pH 1.2 (HCl) and pH 7.2 phosphate buffer (PB) solutions was validated and verified for linearity, intra-day and inter-day precision, accuracy, recovery and specifity by UV spectroscopy (Shimadzu UV-1700 Spectrophotometer, Japan). Each study was replicated 6 times [13].

To achieve this, UV spectra of KT were taken at each dissolution medium by scanning samples from 180 nm to 400 nm wave lengths at the absorbance mode of the apparatus. Absorption spectra of KT showed $\lambda_{max}$ at 323 nm at each of the media.

***Linearity***

The linearity of the method was evaluated by standard linear regression analysis. 2, 4, 6, 8, 10 and 12 µg/mL standard KT solutions in dissolution media were prepared by proper dilutions of 1000 µg/mL stock KT solutions. Absorbance of standard solutions was measured at 323 nm in distilled water, pH 1.2 (HCl) and pH 7.2 (PB) solutions. Calibration curves were constructed by plotting concentration versus absorbance using linear regression analysis.

***Precision, accuracy and recovery***

Intra-day and inter-day precision and the accuracy of the method were calculated from data obtained during a 2-day validation. The precision of the method was determined by intra-day repeatability and inter-day intermediate precision. KT solutions in dissolution medium (2, 4, 6, 8, 10 and 12 µg/mL) were prepared by proper dilutions of the stock KT solution (1000 µg/mL) six times on the same day. Intermediate precision was assessed by comparing the assays on different days (2 days, n = 3 at each concentration).

***Precision***

Precision was expressed as the relative standard deviation (RSD, %). Accuracy was expressed as the mean relative error (MRE, %). Recovery (%) was also calculated from the amount of drug found.

***Specificity***

The specificity of the method was investigated for demonstrating that the constituent in the formulations did not interfere quantification of KT. For this purpose, placebo tablets were crushed and then powdered in a mortar. 0.5 g powder was weighed into a 250 mL volumetric flask. 100 mL medium was added and the mixture was homogenized in an ultrasonic bath for 15 min. The mixture was diluted to 250 mL with additional medium. 0.2 mL supernatant was withdrawn, diluted to 10 mL with the medium and assayed at 323 nm. This study was repeated for each tablet series in three dissolution media.

**Determination of content uniformity of matrix tablets**

Tablets were powdered in a mortar. Powder containing KT equivalent to 40 mg were taken into a 100 mL volumetric flask and diluted with 50 mL water. The suspension was kept in an ultrasonic bath for 5 min. The suspension was filtered through a S & S5893 blue ribbon filter paper (Schleicher und Schuell, Germany) after being diluted to 100 mL with additional medium. Supernatant (2 mL) was withdrawn and diluted properly. The final solution was assayed by UV spectroscopy. Each study was replicated 6 times. Thus, percent of KT content to the target content (40 mg) per dosage unit was calculated to determine content uniformity according to The United States Pharmacopoeia 28 and National Formulary 23 (USP 28-NF 23) [14].

***In vitro* drug release studies**

The release of KT from tablets was studied according to the USP 32 Type II (paddle method) at 37 ± 0.5 $^{o}$C in 900 mL distilled water, pH 1.2

(HCl) and pH 7.2 (PB) solutions at 50 rpm rotation speed by using a Varian dissolution apparatus (U.S.A.). One milliliter samples were taken by autosampling unit at predetermined time intervals and diluted to 10 mL and filtered through the S&S5893 type blue ribbon filter paper. Solutions were assayed by UV spectroscopy at 323 nm.

The kinetics of drug release from matrix tablets in three dissolution media were evaluated by zero-order, first-order and Higuchi root-square models [9,15]. The dissolution data were also evaluated according to Korsmeyer-Peppas equation (exponential equation) since these models fail to explain drug release mechanism in case of swelling along with gradual erosion of the matrix due to hydration [16,17]. Korsmeyer-Peppas equation is often used to describe drug release behaviour from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved.

### Statistical analysis

*In vitro* drug release data were evaluated using GraphPad Prism 5 software and one-way ANOVA to determine differences among release data. $P < 0.05$ was set as the level of significance.

## RESULTS

### Physical properties of matrix tablets

Placebo tablets displayed flow and compression quality as “fair to passable” and “good” except a formulation containing 30 % XG (XG-30) showed poor characteristics (Table 2). However, addition of KT altered flowability and compressibility properties of powders with very poor flow and compression quality. “Poor” or “very poor” characteristics were observed with decrease in wax or polymer concentrations in general. In the case of bulk KT, the weakest CI and HR values were obtained.

Tablet weights were between 176.7 ± 0.001 mg and 180.7 ± 0.001 mg for placebo tablets and, 177.2 ± 0.001 mg and 182.8 ± 0.002 mg for KT tablets. The lowest tensile strength (0.37 Mpa) was obtained with KT tablets (Pr-30) based on Precirol at 30 % concentration. Friability values obtained were all below 0.5 %. Except for the tablet formulations PSA-30, PSA-40, SA-30 and SA-40, all the tablets did not disintegrate during 10 h in the disintegration test performed in distilled water at 37 ± 0.5 $^{o}$C. Formulations PSA-30, PSA-40, SA-30 and SA-40 disintegrated after 8, 7, 6 and 6 h, respectively.

**Table 2:** Compression properties of powders and physical characterization of placebo and ketorolac tromethamol (KT) matrix tablets

| Formulation | | CI (n = 10) | Flow and compression quality | HR (n = 10) | Weight ± SD (mg) (n = 20) | Hardness (N) (n = 10) | Tensile strength (Mpa) |
|---|---|---|---|---|---|---|---|
| Placebo tablets | PCo-30 | 17.2 | Fair to passable | 1.20 | 179.5 ± 0.001 | 69.0 ± 1.47 | 1.49 |
| | PCo-40 | 15.4 | Good | 1.18 | 179.9 ± 0.001 | 53.1 ± 1.67 | 1.10 |
| | PPr-30 | 17.3 | Fair to passable | 1.21 | 180.7 ± 0.001 | 71.5 ± 2.45 | 1.48 |
| | PPr-40 | 13.3 | Good | 1.15 | 177.9 ± 0.001 | 64.9 ± 2.55 | 1.38 |
| | PSA-30 | 15.1 | Good | 1.18 | 179.6 ± 0.001 | 96.7 ± 1.47 | 2.04 |
| | PSA-40 | 20.5 | Fair to passable | 1.26 | 179.2 ± 0.001 | 93.5 ± 1.28 | 1.94 |
| | PHPMC-30 | 18.4 | Fair to passable | 1.23 | 176.7 ± 0.001 | 169.0 ± 9.22 | 3.86 |
| | PHPMC-40 | 13.8 | Good | 1.16 | 180.2 ± 0.001 | 146.6 ± 0.10 | 3.37 |
| | PXG-30 | 22.2 | Poor | 1.29 | 179.3 ± 0.001 | 117.3 ± 0.10 | 2.71 |
| | PXG-40 | 21.1 | Fair to passable | 1.27 | 179.0 ± 0.001 | 93.7 ± 0.10 | 2.13 |
| KT tablets | Co-30 | 20.6 | Fair to passable | 1.26 | 178.9 ± 0.003 | 68.7 ± 4.51 | 1.44 |
| | Co-40 | 25.5 | Fair to passable | 1.34 | 182.0 ± 0.002 | 68.8 ± 3.43 | 1.40 |
| | Pr-30 | 28.4 | Poor | 1.40 | 182.2 ± 0.001 | 44.6 ± 3.73 | 0.86 |
| | Pr-40 | 25.2 | Fair to passable | 1.34 | 177.2 ± 0.001 | 20.2 ± 2.84 | 0.37 |
| | SA-30 | 30.8 | Poor | 1.45 | 179.1 ± 0.002 | 48.1 ± 20.59 | 0.92 |
| | SA-40 | 33.0 | Poor | 1.49 | 179.0 ± 0.003 | 63.4 ± 22.85 | 1.31 |
| | HPMC-30 | 19.3 | Fair to passable | 1.23 | 178.9 ± 0.001 | 61.7 ± 4.71 | 1.25 |
| | HPMC-40 | 17.8 | Fair to passable | 1.22 | 182.8 ± 0.002 | 96.3 ± 10.00 | 1.98 |
| | XG-30 | 32.0 | Very poor | 1.47 | 178.2 ± 0.001 | 66.5 ± 5.20 | 1.49 |
| | XG-40 | 26.3 | Poor | 1.36 | 179.8 ± 0.002 | 33.4 ± 4.41 | 0.68 |
| | Bulk KT | 36.6 | Very poor | 1.58 | - | - | - |

**Validation of spectrophotometric analysis**

The representative linear equation was A = aC + b, where C is the concentration, A the absorbance, a is the slope, and b is the intercept. In the current method, regression equations were A = 5.435C – 0.001 with $r^2$ = 0.9998 in distilled water; A = 2.544C – 0.001 with $r^2$ = 0.9972 in pH 1.2 (HCl) solution; A = 5.485C – 0.001 with $r^2$ = 0.9999 in pH 7.2 (PB) solution.

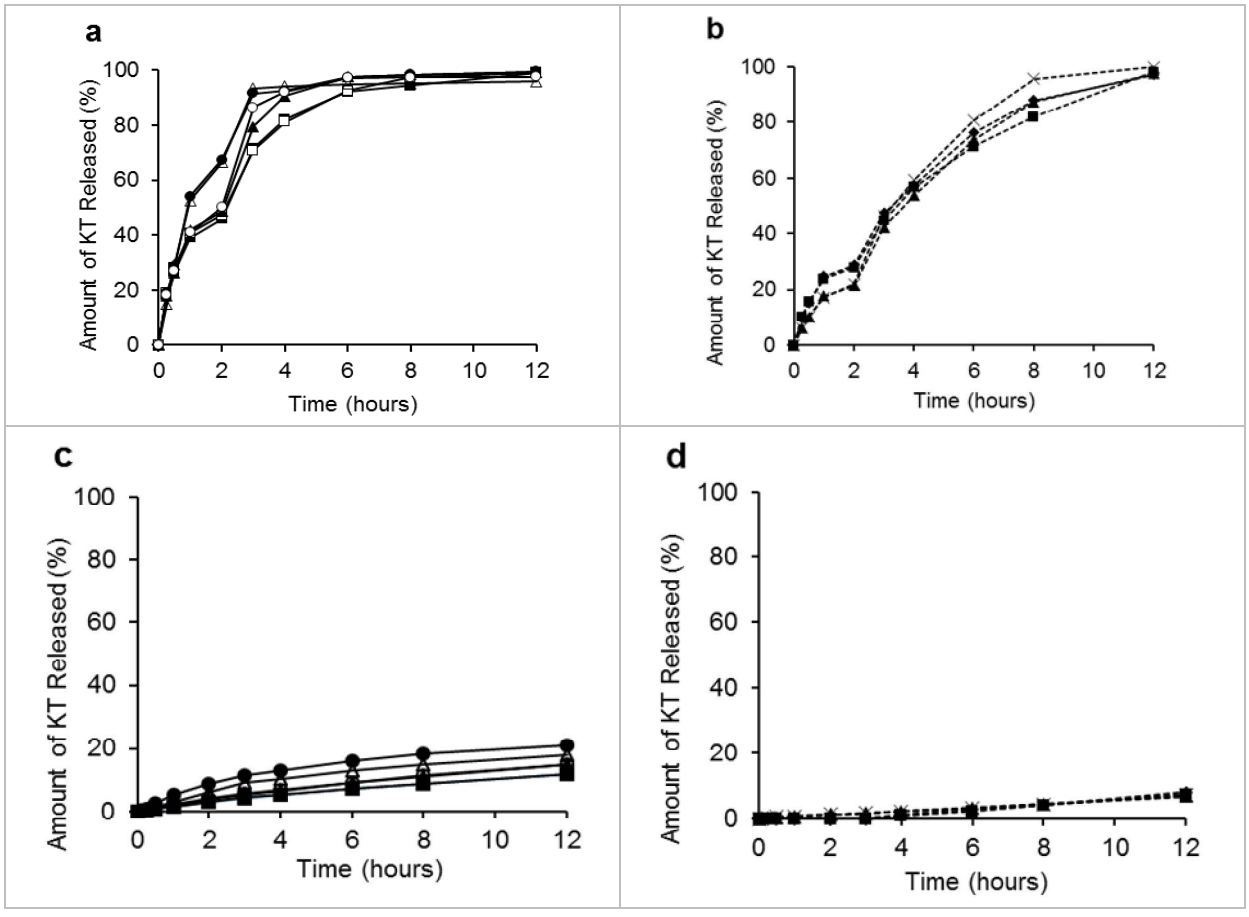
R.S.D. values obtained from intra-day and inter-day precision of the analytical method were between 0.05 - 1.50 % in all media. Accuracy of the method was also expressed here as MRE; lower than 2 %, between 0 % and 1.67 %. Recovery of KT was between 97.25 and 100.00 %. All other ingredients were found not to display absorbance at 323 nm which was maximum wavelength for KT in dissolution media indicating specificity of the method. It was demonstrated that they would not interfere quantification of KT by UV spectroscopy.

**Content uniformity of matrix tablets**

KT content of matrix tablets was between 38.85 ± 0.25 mg and 39.96 ± 0.08 mg. Thus, percent of KT content to the target content per dosage was between 97.125 % and 99.90 %.

***In vitro* drug release from matrix tablets**

An insignificant difference was observed between KT release profiles of the matrix tablets prepared with HPMC (HPMC-30 and HPMC-40) and XG (XG-30 and XG-40) in water ($p > 0.05$). Those formulations displayed sustained drug release when matrix tablets prepared with waxes gave faster drug release ($p < 0.05$) (Fig. 1 and Table 3). On the other hand, the slowest drug release rates were obtained from matrix tablets in pH 1.2 among the other media ($p < 0.05$). Lower than 8 % of KT was released from formulations prepared with HPMC and XG at the 12th hour ($p > 0.05$) when tablets prepared with Compritol, Precirol and SA displayed higher drug release between 11.72 and 20.93 % at pH 1.2 ($p > 0.05$). In the case of pH 7.2 (PB) solution, the slowest drug release profile was obtained from tablets prepared with HPMC at 40 % (HPMC-40) and XG at 30 % (XG-30) followed by formulations HPMC-30, XG-40, Co-30, Co-40, Pr-30, SA-40, Pr-40 and SA-30.



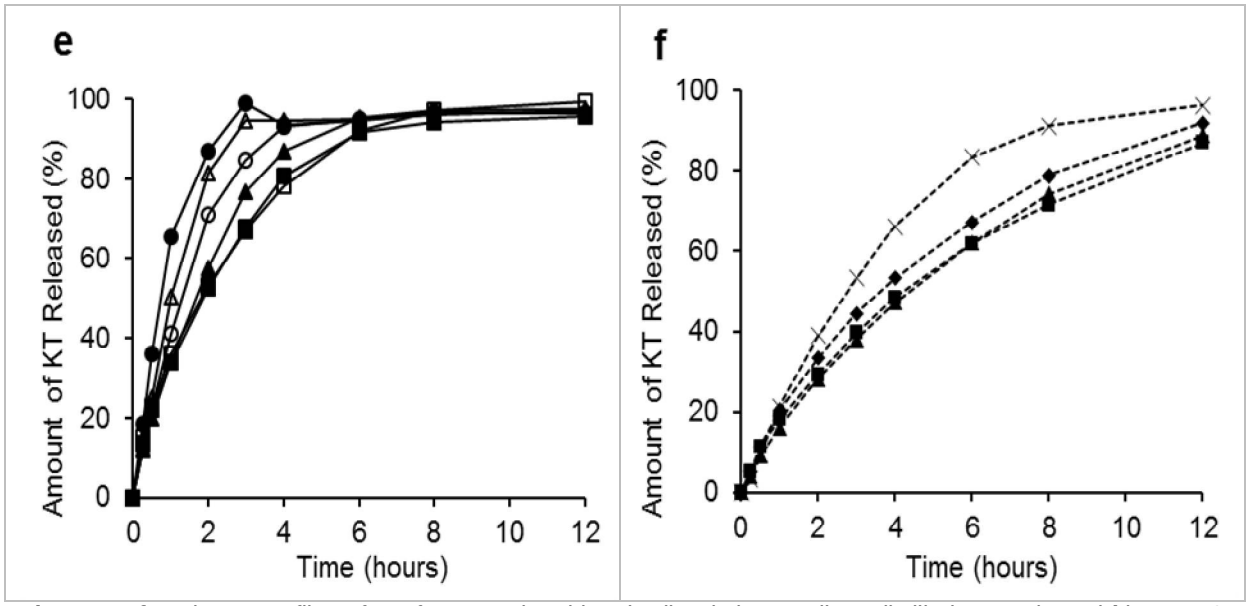



**Figure 1a-f:** Release profiles of KT from matrix tablets in dissolution media – distilled water (**a** and **b**), pH 1.2 (HCl) (**c** and **d**) and pH 7.2 (PB) (**e** and **f**) solutions; , −■ − = Co-30, −□− = Co-40, −▲− = Pr-30, −Δ− = Pr-40, −●− = SA-30, −○− = SA-40, --♦-- = HPMC-30, --■-- = HPMC-40, --▲-- = XG-30, --x-- = XG-40

**Table 3:** Kinetic modelling of drug release from ketorolac tromethamol (KT) matrix tablets in distilled water, pH 1.2 and pH 7.2, respectively

| *Formulation* | *Zero order* | | *First order* | | *Higuchi model* | | *Exponential (Korsmeyer – Peppas model)* | | *Order of release (Korsmeyer – Peppas model)* | *Diffusion rate (g/h) x $10^3$* |
|---|---|---|---|---|---|---|---|---|---|---|
| | $r^2$ | $K_0$ | $r^2$ | $K_1$ | *r* | *D* | $r^2$ | *n* | | |
| | 0.774 | 6.96 | 0.654 | 0.12 | 0.916 | 29.91 | 0.966 | 0.465 | Non-Fickian | 8.255 |
| Co-30 | 0.979 | 0.98 | 0.722 | 0.25 | 0.991 | 3.90 | 0.995 | 0.903 | n/a | 0.977 |
| | 0.749 | 7.05 | 0.605 | 0.14 | 0.908 | 30.69 | 0.961 | 0.536 | Non-Fickian | 7.960 |
| | 0.782 | 6.92 | 0.661 | 0.12 | 0.922 | 29.72 | 0.970 | 0.451 | Non-Fickian | 8.250 |
| Co-40 | 0.978 | 0.97 | 0.727 | 0.23 | 0.992 | 3.86 | 0.994 | 0.844 | Non-Fickian | 0.985 |
| | 0.788 | 7.25 | 0.637 | 0.13 | 0.934 | 31.19 | 0.973 | 0.517 | Non-Fickian | 8.258 |
| | 0.701 | 7.01 | 0.601 | 0.12 | 0.866 | 30.79 | 0.947 | 0.479 | Non-Fickian | 8.271 |
| Pr-30 | 0.984 | 1.21 | 0.102 | 0.23 | 0.989 | 4.81 | 0.998 | 0.821 | Non-Fickian | 1.235 |
| | 0.692 | 7.24 | 0.559 | 0.14 | 0.869 | 32.07 | 0.941 | 0.573 | Non-Fickian | 8.129 |
| | 0.548 | 5.97 | 0.445 | 0.11 | 0.751 | 27.61 | 0.868 | 0.471 | Non-Fickian | 7.983 |
| Pr-40 | 0.914 | 1.49 | 0.614 | 0.24 | 0.992 | 6.13 | 0.961 | 0.912 | n/a | 1.498 |
| | 0.504 | 6.08 | 0.409 | 0.12 | 0.712 | 28.53 | 0.841 | 0.530 | Non-Fickian | 8.098 |
| | 0.602 | 6.20 | 0.494 | 0.10 | 0.798 | 28.21 | 0.900 | 0.445 | Fickian | 8.292 |
| SA-30 | 0.881 | 1.67 | 0.571 | 0.21 | 0.983 | 6.99 | 0.935 | 0.821 | Non-Fickian | 1.744 |
| | 0.438 | 5.01 | 0.367 | 0.09 | 0.645 | 24.02 | 0.800 | 0.402 | Fickian | 8.015 |
| | 0.808 | 6.77 | 0.574 | 0.12 | 0.829 | 30.15 | 0.934 | 0.473 | Non-Fickian | 8.136 |
| SA-40 | 0.975 | 1.20 | 0.725 | 0.22 | 0.995 | 4.81 | 0.994 | 0.807 | Non-Fickian | 1.236 |
| | 0.593 | 6.63 | 0.478 | 0.13 | 0.793 | 30.28 | 0.895 | 0.552 | Non-Fickian | 8.022 |
| | 0.920 | 7.83 | 0.756 | 0.17 | 0.979 | 31.93 | 0.986 | 0.614 | Non-Fickian | 8.093 |
| HPMC-30 | 0.942 | 0.67 | 0.930 | 0.19 | 0.804 | 2.47 | 0.594 | 0.465 | Non-Fickian | 0.661 |
| | 0.924 | 7.41 | 0.675 | 0.19 | 0.995 | 30.39 | 0.983 | 0.729 | Non-Fickian | 7.673 |
| | 0.944 | 7.68 | 0.778 | 0.17 | 0.987 | 31.02 | 0.987 | 0.601 | Non-Fickian | 8.173 |
| HPMC-40 | 0.927 | 0.62 | 0.850 | 0.18 | 0.776 | 2.25 | 0.477 | 0.413 | Fickian | 0.611 |
| | 0.942 | 6.95 | 0.698 | 0.19 | 0.998 | 28.28 | 0.986 | 0.717 | Non-Fickian | 7.260 |
| | 0.929 | 8.42 | 0.753 | 0.09 | 0.973 | 34.04 | 0.982 | 0.755 | Non-Fickian | 8.129 |
| XG-30 | 0.999 | 0.54 | 0.789 | 0.27 | 0.942 | 2.09 | 0.998 | 0.951 | n/a | 0.556 |
| | 0.948 | 7.36 | 0.695 | 0.21 | 0.997 | 29.80 | 0.988 | 0.794 | Non-Fickian | 7.421 |
| | 0.898 | 8.90 | 0.733 | 0.22 | 0.959 | 36.36 | 0.977 | 0.784 | Non-Fickian | 8.325 |
| XG-40 | 0.991 | 0.56 | 0.834 | 0.11 | 0.912 | 2.15 | 0.988 | 0.864 | Non-Fickian | 0.594 |
| | 0.843 | 8.25 | 0.578 | 0.22 | 0.961 | 34.81 | 0.947 | 0.880 | Non-Fickian | 8.029 |

$r^2$: determination coefficient; $K_0$: zero order release constant (mg%/h); $K_1$: first order release constant ($h^{-1}$); *D*: diffusion coefficient (mg%/$h^{1/2}$); *n*: release exponent; *n/a*: not applicable

## DISCUSSION

Content uniformity of KT tablets were in limits (85-115 % of target content), although powders of some formulations had poor flow and compression quality. Addition of KT herewith decrease in Avicel concentration may cause that. Because, Avicel presents acceptable flow properties required for succesful large-scale tableting [18]. The physical characteristics of the placebo and KT tablets met compendial requirements, indicating homogeneous blend of ingredients and sufficient powder characteristics during the large scale compression. Tensile strength and friability of the tablets lower than 0.5 % indicated high mechanical strength of all the placebo and KT tablets. The satisfactory characteristics of the tablets can also be partially attributed to the addition of PVP-K 90, which displayed a good binding effect for formulations at 5 % concentration [18,19].

Validation of a quantification method is the process used to confirm that the analytical procedure employed is suitable for its intended use [13]. Before starting to study on determination of content uniformity and drug release profiles of the matrix tablets, quantification method of KT by UV spectroscopy was validated in dissolution media. The validation process demonstrated that the results attained were fit for their intended purpose and performance verification of instrumentation and equipment is concerned with ensuring that they are performing correctly.

Release profiles demonstrated a pH-dependent mechanism of KT release from matrix tablets (Fig. 1). Since ketorolac is a weak acid with a carboxylic acid group, the influence of an acid pH on solubility and dissolution is the main contributing factor. Solubility of KT were reported as 0.896, 0.315 and 0.886 mg/mL in distilled water, pH 1.2 (HCl) and pH 7.2 (PB) solutions, respectively [20]. Increase in pH resulted in an increase in KT release rates from all formulations

As can be seen in this study , when a system composed of hydrophylic polymers like HPMC and XG gets in contact with aqueous medium, the medium difuses into the system [16,17,21]. Polymer at surface turns into a gel at first. When transfer of medium into the system continues, gel layer gets thicker and the system swells. In the meantime, outer gel layer continually regenerates. Drug release from KT matrix tablets fit the Higuchi kinetic model in general (Table 3). The release exponent of Korsmeyer-Peppas model (n) was taken into consideration as the parameter which is dependent on the release mechanism. Therefore, it was used to characterize drug release mechanism from matrix tablets. $n \leq 0.45$ corresponds to the Fickian diffusion release (case I diffusion), $0.45 \leq n < 0.89$ to the non-Fickian (anomalous transport), $n = 0.89$ to the zero order release kinetics (case II), and $n > 0.89$ to the supercase II transport in case of cylindrical matrix tablets [16,17]. The mechanism of drug release up to 60 % was Fickian (diffusion controlled release). The non-Fickian kinetics correspond to coupled diffusion/polymer relaxation that was clear with HPMC and XG tablets as could be expected.

In the case of waxy tablets, differences were detected only up to the 4th h and then, tablets displayed the same profiles. More than 90 % of KT was released from tablets in distilled water and pH 7.2 (PB) solution at about the 6th h. The slowest release rate was observed with Compritol tablets followed by Precirol and SA. Release of KT from waxy tablets was also based on the diffusion/erosion mechanism in general.

## CONCLUSION

An optimal formulation should be able to yield lower dose frequency and reduce dose-related side effects of drugs when administered orally. The matrix tablets of KT prepared with HPMC (30 or 40 %) displayed controlled drug release as well as the optimal compression properties required for large-scale production. However, further *in vivo* studies are required to demonstrate the effectiveness of the formulations.

## DECLARATIONS

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***Conflict of Interest***

No conflict of interest associated with this work.

***Contribution of Authors***

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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