Formulation optimization, *in vitro* characterization and stability studies of sustain release tablets of Ketoprofen

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Abstract: The aim of the current study was to formulate sustain release (SR) tablets of ketoprofen. Five batches (batch I -V) of matrix based ketoprofen tablet were prepared by dry granulation method using hydroxyl propyl methyl cellulose (15000cps). Compatibility of formulation excipients with drug was explored through FT-IR technique. Various physical and chemical parameters of all tablet batches were evaluated with multi-point dissolution profile (for 24hrs) for formulation optimization. Release kinetics of trials was estimated by model dependent and independent methods. Formulations having excellent quality attributes were then compared with marketed ketoprofen SR tablets. Accelerated stability study was also conducted to compute the shelf life of the optimized formulation. FT-IR scans illustrated the compatibility of ketoprofen with all tablet excipients. On the basis of testing results and controlled release pattern batch II was set to be an optimized trial having shelf life of 37 months. All trial batches (batch I-V) and the marketed brand exhibited highest linearity towards zero order and Korsmeyer-Peppas model with non-fickian anomalous transport (n=0.541-0.655).

Keywords: Ketoprofen, sustained release, dissolution profile, methyl cellulose.

INTRODUCTION

Ketoprofen 2-(3-Benzoyl phenyl) propionic acid derivative is commonly used as analgesic, antipyretic and anti-inflammatory agent. Being a non-steroidal anti-inflammatory drug, it inhibits the biosynthesis of prostaglandins resulting in reduce sensitization of tissues to pain mediators such as 5-hydroxtryptamine, histamine and kenins (Ong and Seymour, 2003). Therefore, drug efficacy has been proved for arthritis, toothache, primary dysmenorrheal and post-operative gynecological surgery pain (Kosjek *et al.,* 2011). Initial oral dose for arthritis is 75 mg thrice a day or 50 mg four times daily, augmented up to 300 mg daily in divided doses. A dose of 25-50 mg, 6 to 8 hourly has been advised for the relief of pain (Sarzi-Puttini *et al*., 2010).

Immediate release (IR) tablet dosage is still valuable due to ease of administration with rapid action. However, IR formulations have documented to be problematic especially in elder patients with multiple diseases due to repeated ingestion of units. Conversely, controlled/sustain release dosage is considered to be a substitute to overcome the issues of dose frequency and so improving the patient compliance. Additionally the controlled release pattern provides better drug plasma profile with reduced side effects (Azmy et al., 2017). For developing such modified release system, polymers are the integral component that delays the release of drug to a desirable time interval. Selection, nature and the appropriate amount of retardant play significant role in product optimization of CR dosages. A large variety of polymers from natural, synthetic and semi synthetic sources are available classified on the basis of their nature of solubility as hydrophilic and hydrophobic polymers. Hydrophilic retardants (natural gums, cellulose esters and hydroxyl propyl methyl cellulose HPMC) and hydrophobic systems (Pandey *et al*., 2019) (methacrylic resin, ethyl cellulose and glyceryl monostearate) are capable of forming controlled matrixes, hence frequently utilized for developing diverse controlled release products (Ma *et al.,* 2017; Lanchis *et al.,* 2017).

This study was aimed to formulate ketoprofen sustained release (SR) matrix tablets that could control the steady drug release up to 24 hrs. Compatibility of excipients with ketoprofen was assessed prior to compression by FT-IR method. Tablets were prepared by dry granulation using various concentrations of hydrophilic polymer methocel 15000 cps grade. Physico-chemical testing with multi-point dissolution was performed for product optimization. Optimized trial(s) were subjected to stability studies and shelf life was estimated by assay data.

MATERIALS AND METHODS

Ketoprofen (BEC Chemicals Mumbai India), methocel ® 15000 Cps (Colorcon, England), magnesium stearate

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(Dow Chemical, USA), collidal silicon dioxide (Henan Xunyu Chemicals Co., Ltd), avicel® PH 102 (FMC Corporation, USA), sodium hydroxide, hydrochloric acid and potassium dihydrogen phosphate (Merck, Darmstadt, Germany).

Compatibility studies

Interaction of drug-polymer was determined by taking the infra-red spectra using KBr disc preparation separately for drug and polymers as well as for drug-polymer blends.

Preparation of tablets

Five batches (I to V) of ketoprofen matrix based SR tablets were formulated by dry granulation technique of compression using various concentrations of hydroxy propyl methyl cellulose (08-20%) 15000 cps grade and microcrystalline cellulose (avicel PH102 18-30%). While fixed quantities of colloidal silicon dioxide, magnesium stearate and ketoprofen were added respectively as glidant, lubricant and therapeutic agent. The formulation composition of batches is given in table 1.

Ketoprofen was mixed geometrically with polymer HPMC 15000 cps, collidal silicon dioxide and avicel PH 102 for 15 minutes. Slugs were prepared, crushed and mixed with magnesium stearate for 5 minutes. The powder mix was then subjected to the compression using Manesty rotary tablet press with 9.0 mm round, flat punches.

Physical evaluation of ketoprofen tablets

Thickness, diameter, weight variation, hardness and friability of all compressed tablets were determined. Weight variation was carried out by weighing 20 individual tablets of each formulation through electronic analytical balance (Sartorius CP 224S, Germany). Hardness tester (Fujiwara Seisakusho, Ogawa Seiko Co Ltd, Tokyo, Japan) and vernier caliper (CD-6, CSX, Mitutoyo, Japan) were used to assess hardness and thickness of tablets, respectively.

Friability was determined on twenty tablet units for each batch, weighed and revolved for 4 minutes at 25 rpm in double drum friabilator (Erweka GmbH D-63150, Husenstamn, Germany). Final weights were noted after de-dusting the units and the percent friability was calculated (USP 36, 2013).

Pharmaceutical assay

Ketoprofen SR tablets were tested for content by HPLC technique (LC-10AT, Shimadzu, Japan) after performing the system suitability test. The system was equipped with 4.6mm × 25cm, 5µm packing L1 (C18) column maintained at temperature of 30±2ºC; UV detector was used at 254nm. Flow rate was 1.2mL/min with the injection volume was 20µL. Mobile phase was a mixture of acetonitrile, water and glacial acetic acid (45:55:1 v/v).

Twenty tablets from each batch were pulverized to fine powder. An accurately weighed quantity of tablet powder (equivalent to 50mg drug) was transferred to 50mL volumetric flask and make up volume up with mobile phase to prepare the stock solution. Drug solution was sonicated for 5 minutes followed to 5 minutes stirring. From the stock solution, 1.2mL was taken and diluted to 50mL with diluents and then filtered. Standard and test solutions of ketoprofen were prepared in the same manner and injected to measure peak areas.

Multiple point dissolution testing

USP dissolution apparatus II at 75rpm (DT 600, Erweka, Japan) was used to study ketoprofen release profiles. Six tablets were analyzed from each formulation lot. Each tablet was placed in 900mL dissolution media maintained to pH 2.5 and 37±0.5°C temperature. Two samples of 5 ml were taken after 60 and 120 min time points. After two hours, dissolution medium was replaced with phosphate buffer pH 7.4 and dissolution testing was then continued for 24 hours. Samples were drawn, filtered and analyzed at 258nm through UV-Vis Spectrophotometer (UV-1800, Shimadzu, Kyoto, Japan).

Comparison of dissolution profile

In vitro dissolution profiles of ketoprofen SR tablets were studied by various models dependent and independent methods.

Model dependent approach

Data of in-vitro dissolution testing were fitted to different kinetic models proposed by researchers in past (Shoaib *et al.,* 2010; Costa & Lobo, 2001; Zafar *et al.,* 2013). The applied models were zero order (eq. 1), first-order (eq. 2), Higuchi's (eq. 2), Hixson–Crowell (eq. 4), Korsmeyer and Peppas models (eq. 5,6)

$$Q_t = Q_o + k_o t \quad (1)$$

Where Q_o and Q_t represents the initial amount of drug in dosage form and amount released at time t, respectively and K_o is a zero-order rate constant

$$LogQ_t = LogQ_0 - \frac{kt}{2.303} \quad (2)$$

Here, k is the first order rate constant.

$$Q = K_H t^{\frac{1}{2}} \quad (3)$$

Higuchi constant is represented by k_{Hz}

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} \times t \quad (4)$$

K_{HC} is Hixson-Crowell rate constant

$$M_t/M_\infty = Kt^n \quad (5)$$

$$Log\left(M_t/M_\infty\right) = LogK + n\,log\,t \quad (6)$$

M_t/M_∞ is drug released fraction, K is constant and n indicates release mechanisms.

Table 1: Formulation Composition of ketoprofen SR tablets

Formulation	Ketoprofen (mg)	Methyl Cellulose (mg)	Collidal Silicon Dioxide (mg)	Microcrystalline Cellulose (mg)	Magnesium Stearate (mg)
Batch I	200.00	65.00	0.50	58.00	1.5
Batch II	200.00	55.00	0.50	68.00	1.5
Batch III	200.00	45.00	0.50	78.00	1.5
Batch IV	200.00	35.00	0.50	88.00	1.5
Batch V	200.00	25.00	0.50	98.00	1.5

Table 2: Physico-chemical evaluations of ketoprofen matrix tablets.

Formulation Code	Thickness (mm) (Mean ± SD)	Hardness (Kg/cm^2) (Mean ± SD)	Diameter (mm) (Mean ± SD)	Friability (%) (Mean ± SD)	Uniformity of Weight (mg) (Mean ± SD)	Uniformity of Content (%) (Mean ± SD)
Batch I	3.480±0.153	10.510±0.094	9.003±0.067	0.290±0.174	263.136±1.194	99.996±1.740
Batch II	3.554±0.184	9.817±0.231	9.001±0.189	0.130±0.142	271.470±1.743	100.017±1.083
Batch III	3.561±0.103	9.103±0.174	9.000±0.183	0.131±1.737	278.36 ±0.361	99.982±2.845
Batch IV	3.561±1.638	10.645±1.662	9.001±0.173	0.103±1.731	279.871±1.957	99.900±1.465
Batch V	3.562±1.723	8.389 ± 2.632	9.001±1.811	0.100±0.633	286.37± 1.051	100.063±2.739

Table 3: Fitness of release to various mathematical models

S. No	Models	Parameters	Batch I	Batch II	Batch III	Batch IV	Batch V	Marketed SR
1	Zero-Order	k_0	0.1840	0.122	0.0820	0.059	0.050	0.173
		r^2	0.9846	0.9950	0.9942	0.9799	0.9598	0.9985
2	First-Order	k_1	21.296	5.722	4.388	3.614	3.262	4.115
		r^2	0.4221	0.5467	0.8758	0.8286	0.7930	0.8539
3	Higuchi	k_H	41.794	21.097	17.840	14.748	13.339	16.757
		r^2	0.9524	0.9678	0.9582	0.9743	0.9799	0.9676
4	Korsmeyer-peppas	k_p	44.873	21.248	11.722	10.829	10.446	11.644
		r^2	0.9958	0.9979	0.9938	0.9967	0.9951	0.9975
		N	0.541	0.597	0.655	0.614	0.591	0.636

Table 4: f_1, f_2 and ANOVA of optimized ketoprofen SR Trials

Formulation	f_1	f_2	*P* value
Batch II	9.39	63.17	0.819
Batch III	10.98	58.51	0.774

Table 5: Stability parameters and shelf life of ketoprofen optimized batches

Stability Parameters	Batch II	Batch III
Zero Month		
Physical Features	Complies	Complies
Drug Dissolution	100.73 ±0.73	100.52 ±0.23
Percent Assay	101.36±1.30	101.09±0.53
One Month		
Physical Features	Complies	Complies
Drug Dissolution	100.62 ± 1.73	99.84 ±1.43
Percent Assay	101.04±1.66	100.72±2.30
Three Months		
Physical Features	Complies	Complies
Drug Dissolution	100.20 ±2.01	99.63 ±0.63
Percent Assay	100.88±1.39	100.32±2.54
Six Months		
Physical Features	Complies	Complies
Drug Dissolution	99.83 ±2.41	98.01 ±2.63
Percent Assay	100.11±1.02	100.16± 1.38
Shelf lives (months)	37	35

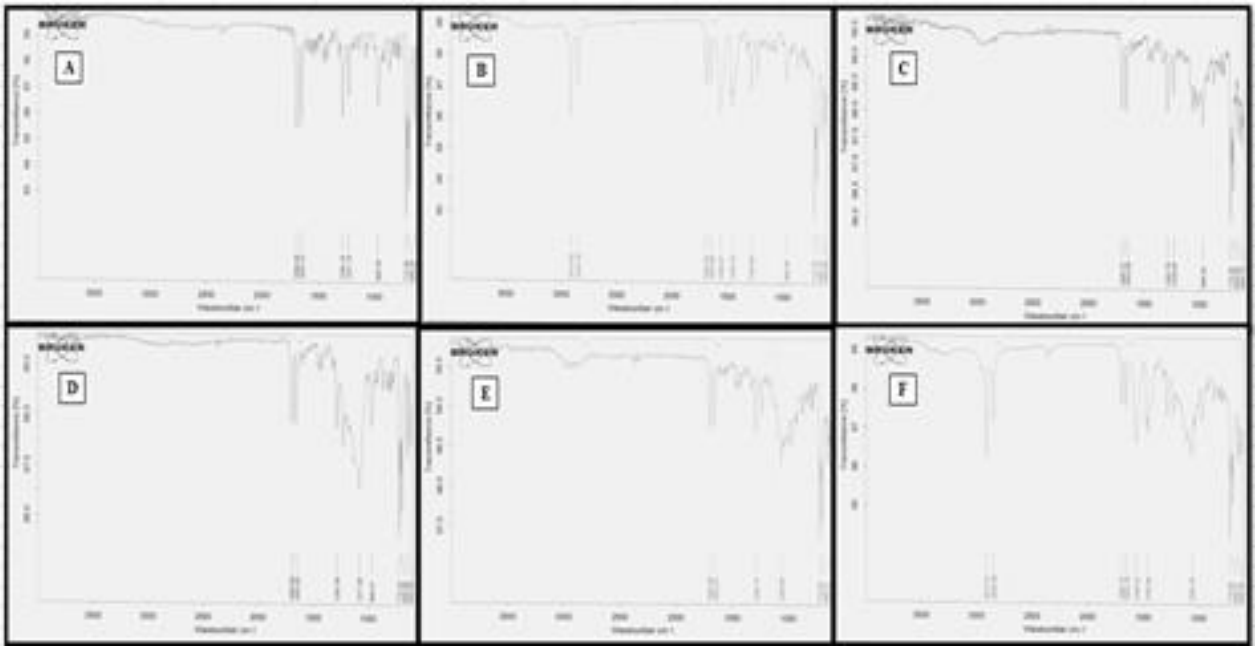

Fig. 1: Interferogram of (A) Ketoprofen (B) Ketoprofen and Magnesium Stearate (C) Ketoprofen and Avicel PH 102 (D) Ketoprofen and Aerosil 200 (E) Ketoprofen and Methocel K15M (F) Ketoprofen with all Excipients

Model independent approach

The difference factor f_1 is basically used to express the sum of vertical distance values between the test and standard values at each dissolution time point. The similarity factor (f_2) is the logarithmic reciprocal square root transformation of one plus the mean squared or average sum of squared differences of percent drug dissolved between the test and the reference products (Moore and Flanner, 1996). Both factors were computed by DD-Solver software as Adds In in Microsoft excels. Following expressions are used for computation;

$$f_1 = \left\{\left[\sum_{t=1}^{n}(R_t - T_t)\right] / \left[\sum_{t=1}^{n} R_t\right]\right\} \times 100 \quad (7)$$

$$f_2 = 50 \times \log\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100. \quad (8)$$

f_1 and f_2 comparison for the optimized formulations (batch II and batch III) were made against commercially available ketoprofen SR tablet.

Statistical comparison

Dissolution profiles of all batches were compared statistically using one way analysis of Variation (ANOVA) at 95% confidence interval and 0.05 level of significance.

Stability testing

Stability studies of ketoprofen trial formulations were performed as per stability protocol of International Conference of Harmonization (ICH Guidelines, 2003). Optimized trial formulations (batch II and batch III) were exposed to accelerated stability conditions of 40˚±2˚C and 75 ±5% humidity for six months. Tablet units were drawn and tested for color, smell, surface texture, dissolution and assay. Shelf lives of trial formulations were determined through incorporating the assay data obtained during storage period into R-Gui version 3.1.2 (stab package) software.

RESULTS

Characteristic peaks and the respective functional groups observed in the FTIR spectra of ketoprofen. FTIR spectra of ketoprofen in the presence of excipients are displayed in fig. 1. Tablets of all the formulated batches were investigated for quality attributes and were found within the limits (table 2).

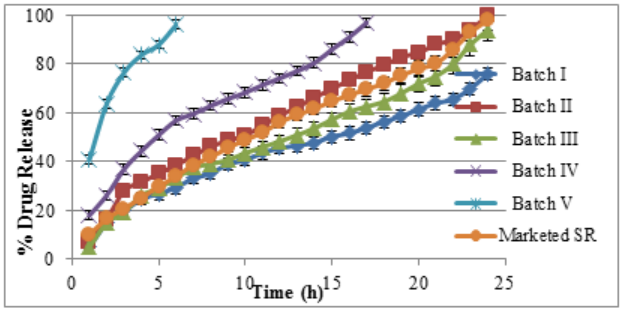

Fig. 2: Dissolution profile of ketoprofen controlled release tablets

Ketoprofen SR batch IV and batch V containing 11% and 8% of K15M respectively showed limited drug retardation, whereas, batch I with 20% HPMC excessively retard the drug release. Batch II and batch III

SR formulations having 17% and 14% of polymer showed desirable controlled drug release profile. Marketed SR tablets of ketoprofen demonstrated 98% drug release in 24 hrs (fig. 2). The results of batch II formulation are found to be very similar with the commercially available SR ketoprofen.

All the trial batches and the marketed brand exhibited highest linearity for zero order and Korsmeyer-Peppas model. The value of "n" for Korsmeyer-Peppas model ranged from 0.54-0.65 for the trial batches and commercial brand (table 3).

Against commercially available ketoprofen SR tablets taken as reference formulation, batch II formulation showed lowest f_1 value (9.39) and the highest f_2 value (63.17). ANOVA confirms the similarity of the release profile for optimized trials and the marketed ketoprofen SR tablets (table 4).

On evaluation of ketoprofen tablets subjected to accelerated stability conditions no significant change in color, physical appearance, drug dissolution and assay was observed and results were within the defined range (table 5). The shelf lives of optimized formulations are given in table 5.

DISCUSSION

The active and excipients used in the formulation of ketoprofen SR tablets were studied by FT-IR for presence of any possible interaction between drug and polymer. Characteristic peaks and the respective functional groups were observed in the FTIR spectra of ketoprofen. The results of our study are in conformance with the earlier published data for the compatibility of ketoprofen and its observed peaks with commonly used pharmaceutical excipients used in the formulation of different solid dosage forms (Tiţa *et al.,* 2011; Vittal *et al.,* 2012). On evaluating FTIR spectra, no drug interaction with the excipients was observed as the particular peaks of ketoprofen remains undisturbed in the presence of excipients (fig. 1).

Tablets from all the formulated batches were investigated for diameter, hardness, thickness, friability, uniformity of content and weight variation. The results of weight variation for the trial formulations exhibited negligible standard deviation reflecting the excellent flowability and appropriate mixing of drug with other formulation ingredients. Tablet dimensions including thickness and diameter of all trial batches was also found within the limits. The hardness of all compressed tablets was found in the range of 8.38 to 10.64 Kg/cm^2 depicting good mechanical strength. The hardness was observed to be increased in a direct proportion with the polymer concentration. Polymers would probably increase the binding properties of API and other adjuvants through entanglement (Sa *et al*., 2019). The friability of all formulations (batch I- V) meets USP friability test criteria (< 1%). The assay of all trial formulations was also found within the limits (table 2). Jan *et al* in 2012 also formulated ketoprofen sustained release tablets with ethyl cellulose and examined all physical and chemical quality features according to the USP methods and were found within the official limits (Jan *et al.,* 2012).

The in-vitro dissolution profile of ketoprofen formulations containing various quantities of HPMC 15000cps and commercially available sustained release tablets (Profenid SR tablet 200mg) manufactured by Sanofi Aventis laboratory, Karachi, Pakistan were evaluated. Ketoprofen formulations (batch IV and batch V) containing 11% and 8% of K15M showed limited sustaining action and maximum drug release is achieved in 17 and 6 hr respectively. Whereas, batch I with 20% HPMC demonstrated excessive drug release retardation and 76% drug is released in 24 hrs. On contrary, the batch II and batch III formulations having 17% and 14% of polymer showed controlled drug release profile and 100% and 94% drug release was observed in 24hrs (fig. 2). The results of dissolution profile reveals that the rate of dissolution of the drug decreased with increase in hydroxy propyl methyl cellulose (HPMC 15000 cps) concentration, indicating that the polymer content is a vital factor for achieving controlled release profile. On the other hand, the commercial SR tablets of ketoprofen demonstrated 98% drug release in 24 hrs (fig. 2). The results of batch II formulation are found to be very similar with the commercially available SR ketoprofen. Saeio and co fellows were developed ketoprofen SR tablets and determined the dissolution characteristics of drug substances from hydrophilic polymer matrix tablets. Likely to our study a linear correlation between the proportions of matrix-forming agents and the extent of dissolution retardation was observed (Saeio *et al.,* 2007).

Dissolution data of ketoprofen compressed tablets with desired drug release profile and commercially available tablets were subjected to different mathematical models to determine drug release kinetics. Solınıs and fellows also used similar models to determine the release kinetics of ketoprofen enantiomers from HPMC K100M matrices (Solınıs *et al.,* 2002). On kinetic model results evaluation, it was observed that all the trial batches and the marketed brand exhibited highest linearity closest to one for zero order and Korsmeyer-Peppas model (table 3). Sankalia and fellows also found maximum linearity for zero order model in HPMC containing formulations (Sankalia *et al.,* 2008). The exponent *"n" i*n Korsmeyer and Peppas model gives an indication of the release mechanism. If the value of *n* is 0.5 then the drug diffuses through and is released from the polymer indicating quasi-Fickian diffusion mechanism. Whereas, non-Fickian solute diffusion

mechanism is followed if n>0.5. However, n=1 is witnessed for zero-order kinetics which is helpful in the formulation of swelling-controlled drug delivery systems. This mechanism of solute transport is known as pseudo-case-II solute transport (Peppas, 1985). In our study, the value of "n" ranged from 0.54-0.65 for the trial batches and commercial brand (table 4) presenting non-Fickian diffusion controlled by both diffusion of the drug through the hydrated matrix and the erosion of the matrix itself (Peppas, 1985). Rao and co scientists also accounted non-Fickian diffusion mechanism for CR cefuroxime axetil (Rao *et al.,* 2013). Famotidine hydrophilic matrix tablets having K4M CR were also analyzed by model dependent methods exhibiting Higuchi, Zero order and Korsmeyer Peppas model having value of "n" depicting anomalous diffusion (Shoaib *et al.,* 2010).

In model independent analysis, difference (f_1) and similarity (f_2) factors were computed by DD-Solver® software (Microsoft Excel adds-In) by pairing up optimized batches (batch II and batch III) with the commercially available ketoprofen SR tablets taken as reference formulation. Batch II formulation showed lowest f_1 value (9.39) and the highest f_2 value (63.17) exhibiting a drug release pattern that was very close to the marketed reference brand (table 5). Similar findings were reported by Sachan and Pushkar where the optimized extended release formulation of diclofenac sodium was compared for drug release behavior with the marketed brands of diclofenac-SR tablets (Sachan and Pushkar, 2009). In many studies difference (f_1) and similarity (f_2) test are used for dissolution profile comparisons (Khan *et al*., 2019; Bushra *et al*., 2018).

FDA emphasizes on stability assessment of newly designed formulations at different climatic conditions to ensure their effectiveness and stability and must remain physio chemically stable throughout their shelf life (Bittorf *et al*., 2019). Accelerated stability testing is most commonly employed to determine the shelf life of pharmaceutical products. In the present study ketoprofen tablets were subjected to accelerated conditions (40±2°C and 75 ± 5% RH). At defined time intervals samples were taken and subjected to stability characterization tests. No significant change in color, physical appearance, drug dissolution and assay was observed and results were within the defined range, confirming the physiochemical stability of optimized formulations and indicative of API compatibility with the other formulation components. The results of stability test are summarized in table 7. Test results were computed in R-Gui software to determine the shelf lives of optimized formulations. A shelf life of 37 months and 35 months were observed for batch II and batch III respectively. Zafar *et al.* reported similar results after performing the long term and accelerated stability studies of ketoprofen tablets for the period of 12 and 6 months, respectively (Farya *et al.,* 2012). Hanif and co fellows also assessed accelerated stability under the ICH guidelines during formulation development and optimization of controlled release nimesulide tablets (Hanif *et al*., 2013).

CONCLUSION

Ketoprofen SR matrix tablets having varying concentration of methyl cellulose were successfully prepared. FTIR studies confirm the experimental conditions and uniform distribution of drug in matrix with no significant interaction between the drug and the polymers. Batch II and batch III formulations endorsed in the sustainability of the drug over 24 hrs following zero order and Korsmeyer-Peppas kinetics. This study illustrates the dose frequency and so would surely enhance the patient compliance. The work can be extended on *in vivo* studies using animal models and/or human volunteers for more accurate and precise results with greater safety parameters.

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