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Research Article

SIMULTANEOUS DETERMINATION OF KETOPROFEN AND METHYL PARABEN, PROPYL PARABEN IN BULK AND FORMULATED GEL BY SPECTROPHOTOMETRY

Patil Pallavi Mangesh[1], Wankhede Sagar Baliram[2], Chaudhari Praveen Digambar[3]
[1]Department of Pharmaceutical Chemistry P. E. Society's Modern College of Pharmacy Yamunanagar, Nigdi, Pune, Maharashtra, India
[2]Department of Pharmaceutical Chemistry Padm, Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, Maharashtra, India
[3]Department of Pharmaceutices, P. E. Society's Modern College of Pharmacy Yamunanagar, Nigdi, Pune, Maharashtra, India
*Corresponding Author Email: pallavipatil_2007@yahoo.com
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ABSTRACT
UV Derivative Spectrophotometric methods for Method I simultaneous determination Method II the first derivative method of Ketoprofen, Methyl Paraben and Propyl Paraben, in Gel was developed in the present work. Spectrophotometric methods for simultaneous determination and the first derivative method of Ketoprofen, Methyl Paraben and Propyl Paraben at 288 nm, 308 nm and 309 nm for KETO, MP and PP respectively. The various parameters were studied according to (ICH). The linearity lies between 10-50 ug/ml for Ketoprofen and 2-10 ug/ml for Methyl Paraben (MP), 0.2-1.0 ug/ml for Propyl Paraben, (PP) for all the two methods. Method II the first derivative method was measured at 306.5 nm, 312.5 nm and 318 nm being Zero crossing point for KETO, MP and PP respectively in Methanol and distilled water (50:50). The proposed method has estimated for method I KETO 100.04 ± 0.372 and MP 99.44 ± 0.112, PP 99.17 ± 0.051 and for Method II KETO 101.17 ± 0.523 and 99.75 ± 0.251, PP 98.17 ± 0.126 in Formulated Gel All the methods showed good reproducibility and recovery with % RSD less than 1.
Keywords: Ketoprofen (KETO) Methyl Paraben (MP) and Propyl Paraben (PP), Simultaneous, Validation.

INTRODUCTION

Ketoprofen, (RS) 2-(3-benzoylphenyl)-propionic acid (chemical formula $C_{16}H_{14}O_3$) shown no Figure 1 belongs to the non-steroidal anti-inflammatory drugs group (NSAID)[1,2]. Recently, there have been a number of reports dealing with various analytical methods for the determination of ketoprofen, such as capillary electrophoresis[3,4], Preservatives Methyl paraben shown no Figure 2 methyl 4-hydroxybenzoate. CAS Number: 99-76-3. Chemical Formula: $C_8H_8O_3$ and Propyl paraben showed no Figure 3 Propyl 4-Hydroxybenzoate. Formulators must be fully aware of the procedure for preservative systems in a product need to be analysed to establish their effectiveness throughout shelf life of the product[5]. Many existing analytical procedures are available in literature for the determination of present preservatives studied, either alone or in combination with other drugs by HPLC and other techniques[6–21]. Steroids, alkaloids, antibiotics, preservatives and vitamins, which are often difficult to separate and analyse by other methods, have been determined successfully HPLC[22]. Literature survey reveals that Ketoprofen can be estimated by spectrophotometry[23], HPLC[24,25] methods individually or in combination with other drugs. Ketoprofen is reported to be estimated by spectrophotometry[26,27] and HPLC[28] individually or in combination with other drugs. However, there is no analytical method reported for the estimation of MP and PP and KETO in a combined dosage formulation. Present work describes two methods for simultaneous estimation of MP and PP and KET in Gel formulation.

MATERIAL AND METHODS

Apparatus

A double beam UV/Visible spectrophotometer, Shimadzu UV- 1700 Pharma spec, was employed with a pair of 1 cm quartz cells for all analytical work.

Reagents and chemicals

Ketoprofen was obtained from Zim Lab. Nagpur, India Methyl Paraben and Propyl Paraben was obtained from Gen Pharmaceuticals Ltd. Pune, Maharashtra, India as gift sample. Sodium hydroxide of analytical grade and double distilled water were used.

Formulation of Ketoprofen Gel

Ketoprofen gel formulation were prepared using 1 % carbopol 940 and as a Gelling agent. Gelling agent was dispersed in a small quantity of distilled water 75 ml and then stored overnight to ensure complete hydration. Ketoprofen in a suitable solvent (water) as added to the dispersion and make up weight with distilled water. Other excipient (methyl paraben 1 % and Propyl paraben 0.1 %) were also added slowly with continuous stirring. In carbopol gels, pH; of the vehicle was brought to neutral by using TEA (Triethanol amine). The final weight of the gel was adjusted to 100 g with distilled water. Entrapped air bubbles were removed by keeping the gels in vacuum desiccators and shown in the Table 1.

Preparation of standard solution

An accurately weighed quantity of 100 mg KETO was transferred to 100 mL volumetric flasks added 10 mg MP and 10 mg PP (in solution form) dissolved and diluted using Methanol: Water (50:50) as solvent up to 50 ml and volume make up with solvent and sonic ate up to 20 minutes. From

this solution, 5.0 mL was transferred to 10.0 mL volumetric flask and diluted to the mark with mobile phase (Concentration 25 µg/mL PP and 25 µg/mL MP, and 1000 µg/mL KETO). Working standard solutions were scanned in the entire UV range to determine the λmax. The λmax of KETO, MP and PP were found to be 288 nm, 308 nm and 309 nm respectively.

Calibration curve

Standard dilutions of each drug were prepared separately having concentrations of 10-50 µg/mL for KETO and 2-10 µg/mL MP and concentration of 0.2 -.1.0 µg/mL for PP. The absorbance of these standard solutions was measured at 288 nm, 308 nm and 309 nm and calibration curve was plotted. The absorptive coefficients of the three drugs were determined using calibration curve shown in Figure 4, 5, and 6 of KETO, MP and PP respectively.

Preparation of sample solutions

An accurately weighed quantity of Gel was weighed equivalent to about 1000 mg of Ketoprofen and 400 mg of Methyl Paraben and 40 mg Propyl Paraben into a 1000-mL volumetric flask. And appropriate amount 500 ml of Methanol: Water (50:50) was then added. The mixture was Ultra sonicated for 30 minutes with heating and allowed to cool at room temperature before adjusting to volume with mobile phase. The organic layer was decant-ted and the extraction procedure was repeated. Working standard solution of 10 µg/mL concentration was prepared by appropriate dilution seven standard dilutions of concentrations of 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 µg/mL was prepared from working standard solution. The absorbance of this sample solution was measured at 288 nm, 308 nm and 309 nm and their concentrations were determined using proposed analytical methods.

Quantitative equations method

Method was based on Quantitative equation method. Primary stock solution was prepared by using Methanol: water (50:50). Calibration curve was prepared by using different concentrations of standard solution. KETO, MP and PP in dosage form were estimated by calibration curve[29,30]. Developed method was validated as per ICH[31-33] guidelines with the help of several parameters like accuracy, precision, LOD, LOQ, and stability.[34]

Estimation in the formulated Gel

An accurately weighed quantity of pre-analysed gel equivalent to about 1000 mg KETO and 400 mg MP and 40 mg PP was transferred individually in nine different 1000 mL volumetric flasks. Then added 500 ml of Methanol was added to each flask and contents of the flask were ultrasonicated for 30 minutes with heating and allowed to cool at room temperature before adjusting to volume with Methanol: water (50:50). The solution was then filtered through what man filter paper no. 41. The solution was further diluted to get different concentrations in the range of 100 ug/ml and 40 ug/ml, 4 ug/ml KETO, MP and PP respectively in the gel. The analysis procedure was repeated three times with the formulation. The result of analysis of the formulation is shown in Table 1.

Method I. Simultaneous equations method and preparation of solutions

Method was based on simultaneous equation method of Vierodt. The method is applicable in the case of sample containing two drugs, each of which absorbs at the λ max of the other. Three equations were developed using absorptive coefficient values as an X component. The content in the mixture was determined by using the following three component equations/ Cramer's rule:

$$X \text{ Component} = \frac{A1(\beta2\gamma3 - \beta3\gamma2) - A2(\beta1\gamma3 - \beta3\gamma1) + A3(\beta1\gamma2 - \beta2\gamma1)}{\alpha1(\beta2\gamma3 - \beta3\gamma2) - \alpha2(\beta1\gamma3 - \beta3\gamma1) + \alpha3(\beta1\gamma2 - \beta2\gamma1)}$$

Similarly, y and z component can be estimated.

Triple combination equations were constructed based upon the fact that the absorbance of the mixture of KETO, MP and PP at 288 nm, 308 nm and 309 nm is the sum of the absorbance at respective wavelengths and the spectra shown in Figure 7. From the absorbance value obtained of all the three λ max, absorptive were calculated and shown in Table 1.

Method II- First order Derivative Spectroscopy

The first order derivative[35] wavelength consider for PP was 318 nm at which KETO and MP was Zero absorbance. The estimation of KETO, MP as carried out at 306.5 nm and 312.5 nm by employing simultaneous equation method at which PP shows Zero absorbance calibration curve were plotted between absorbance observed at first derivative for three days at all the three wavelengths against the conc. In the range of 10-50 ug/ml for Ketoprofen and 2-10 ug/ml for Methyl Paraben (MP), 0.2-1.0 ug/ml for Propyl Paraben, (PP) for all the three methods the estimation of KETO, MP was done framing and solving simultaneous equation by measuring absorbance of KETO at 306.5 nm and MP at 312.5 nm in derivative mode at which PP shows Zero absorbance shown in Figure 8 The conc. Of all three drugs in mixture was calculated by using following equation. Estimation of keto was done by solving the following regration equation:

$$y = 0.039 + 0.0004 \quad \text{---------- for PP}$$

$$C_{MP} = \frac{A2\,ay1 - A1ay2}{Ax2ay1 - ax1ay2} \quad \text{---------- for KETO}$$

$$C_{pp} = \frac{A1\,ax2 - A2\,ax1}{Ax2ay1 - ax1ay2} \quad \text{---------- for MP}$$

Where A1 and A2- absorbance of mixed stud 306.5 and 312.5 respectively; ax1and ax2 absorptivity E (1% 1cm) of MP at KETO 306.5 and 312.5 resp. ay1 and ay2 are the absorptive of MP at 306.5 and 312.5

Method validation

The method validation parameters were checked as per ICH guidelines.

Linearity and range

The linearity for KETO, MP and PP were determined ranging from 5-50 µ/mL and 2-10 ug/ml and 0.2-1.0 ug/ml using working standards.

Precision and Accuracy

The precision of the method was evaluated by interlay and intraday variation studies. In intraday studies, working solutions of standard and sample were analyses thrice in a day. In the interlay variation studies, working solution of standard and sample were Analysed on three consecutive days and percentage relative standard deviation (% RSD) was

calculated. The data is shown in Table 2-7. The accuracy of the method was determined by recovery studies. The recovery studies were performed by the standard addition method at 80 %, 100 % and 120 % level and the percentage recoveries were calculated and are shown in Table 2-4.

Limit of detection and limit of quantitation

LOD was calculated using the following formula and shown in Table 5-8.

$$LOD = 3.3 (\sigma / S)$$

Where, S = slope of calibration curve, σ = standard deviation of the response.

The Limit of Quantification (LOQ) was calculated using the following formula and shown in Table 5-8.

$$LOQ = 10 (\sigma / S)$$

Table 1: Composition of the Carbapol and Pure Drug Ketoprofen As Below

Ingredient	Quantity taken
Ketoprofen	2.5 g
Methyl paraben	1.0 g
Propyl parben	0.1 g
Carbopol (1 %) as gel base	Q S
Double Distilled water	make up to 100 ml
Triethanol amine	Q. S to neutralise gel

Q. S (Quantity sufficient)

Table 2: The Absorptivity Values of KETO, MP and PP in the Proposed Method I

Absorptivity value	288nm	308nm	309 nm
Ax1	0.0611	-	-
Ax2	-	0.0519	-
Ax3	-	-	0.0210
Ay1	0.0526	-	-
Ay2	-	0.0533	-
Ay3	-	-	0.00048
Az1	0.0311	-	-
Az2	-	0.0276	-
Az3	-	-	0.0129

Table 3: The Absorptivity Values of KETO, MP and PP in the Proposed Method II

Absorptivity value	306.5 nm	312.5 nm	318 nm
Ax1	0.0239	-	-
Ax2	-	0.0499	-
Ax3	-	-	0.0278
Ay1	0.0436	-	-
Ay2	-	0.0393	-
Ay3	-	-	0.00233
Az1	0.0193	-	-
Az2	-	0.0189	-
Az3	-	-	0.0169

Whereas; Ax1, Ax2 and Ax3 = are the absorptivity value of KETO at the respective wavelength. Ay1, Ay2 and Ay3 = are the absorptivity value of MP at the respective wavelength. Az1, Az2 and Az3 = are the absorptivity value of PP at the respective wavelength. 1 mg / ml solution was used as primary stock solution. The working solution of 0.1 mg / ml prepared by transferring 5 ml from respective stock solution to a 50 ml volumetric flask and completing to volume with the distilled water. The drug proportion for Q-method was 25 µg/ml KETO, 50 µg/ml MP and 50 µg/ml PP (means the proportion is 25:50:50)

Table 4: Analysis Data of Gel Formulation

Parameter	Method I			Method I		
	KETO	MP	PP	KETO	MP	PP
Drug Content	100.14	99.44	99.17	101.17	99.75	98.17
+-SD	0.372	0.112	0.051	0.523	0251	0.126
% RSD	0.370	0.111	0.049	0.0515	0.252	0.127
S.E	0.111	0.047	0.032	0.228	0.117	0.047

Table 5: Result of Recovery Study for Gel Preparation

Drug	Amount taken (mg)	Amount added		% Recovery	
		%	(mg)	METHOD I	METHOD II
KETO	800	80 %	800.1	100.01	100.08
MP	320	80 %	320.53	100.32	100.09
PP	32	80 %	32.04	100.03	99.64
KETO	1000	100 %	1000	100.03	100.04
MP	400	100 %	398.12	99.90	101.00
PP	40	100 %	39.98	99.94	100.00
KETO	1200	120 %	1198	99.97	99.90
MP	480	120 %	482	100.08	100.00
PP	48	120 %	48.70.	100.48	102.1

Table 6: Validation Parameters for KETO

S. No.	Parameters	Results Method I	Results Method II
1	Absorption (nm)	288 nm	306.5 nm
2	Linearity range (µg/ml)	10-50 ug/ml	10-50 ug/ml
3	Standard regression equation	Y= 0.073 + 0.0151	Y= 0.073 + 0.0151
4	Correlation coefficient (r^2)	r^2 = 0.9927	r^2 = 0.9927
5	A (1 %, 1 cm)	100.29 ± 0.148	100.09 ± 0.111
6	Accuracy (% recovery ± SD)	100.70 ± 0.117	100.86 ± 0.123
7	Precision (% CV) Interlay Intraday	 100.06 ± 100.19 ±	 100.11 ± 100.09 ±
8	LOD	0.022	0.011
9	LOQ	0.031	0.020

Table 7: Validation Parameters for MP

S. No.	Parameters	Results Method I	Results Method II
1	Absorption (nm)	308 nm	312.5 nm
2	Linearity range (µg/ml)	2-10 ug/ml	2-10 ug/ml
3	Standard regression equation	Y= 0.0045 + 0.0068	Y= 0.0045 + 0.0068
4	Correlation coefficient (r^2)	r^2-= 0.9929	r^2-= 0.9929
5	A (1 %, 1 cm)	99.99 ± 0.1315	99.09 ± 0.121
6	Accuracy (% recovery ± SD)	100.29 ± 0.117	100.66 ± 0.143
7	Precision (% CV) Interday Intraday	 101.03 100.29	 100.11 100.01
8	LOD	0.014	0.010
9	LOQ	0.025	0.021

Table 8: Validation Parameters for PP

S. No.	Parameters	Results Method I	Results Method II
1	Absorption (nm)	309 nm	318 nm
2	Linearity range (µg/ml)	0.2-1.0 ug/ml	0.2-1.0 ug/ml
3	Standard regression equation	Y= 0.0116 + 0.0086	Y= 0.073 + 0.0151
4	Correlation coefficient (r^2)	r^2-= 0.9916	r^2-= 0.9927
5	A (1 %, 1 cm)	99.69 ± 0.048	99.89 ± 0.011
6	Accuracy (% recovery ± SD)	99.98 ± 0.117	99.56 ±0.103
7	Precision (% CV) Interlay Intraday	 100.49 100.09	 100.01 100.02
8	LOD	0.010	0.009
9	LOQ	0.013	0.011

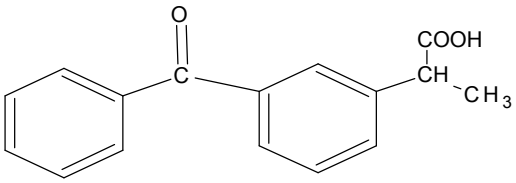

Figure 1: KETOPROFEN

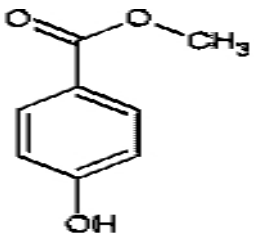

Figure 2: METHYL PARABEN

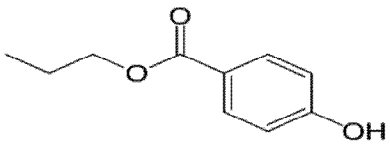

Figure 3: PROPYL PARABEN

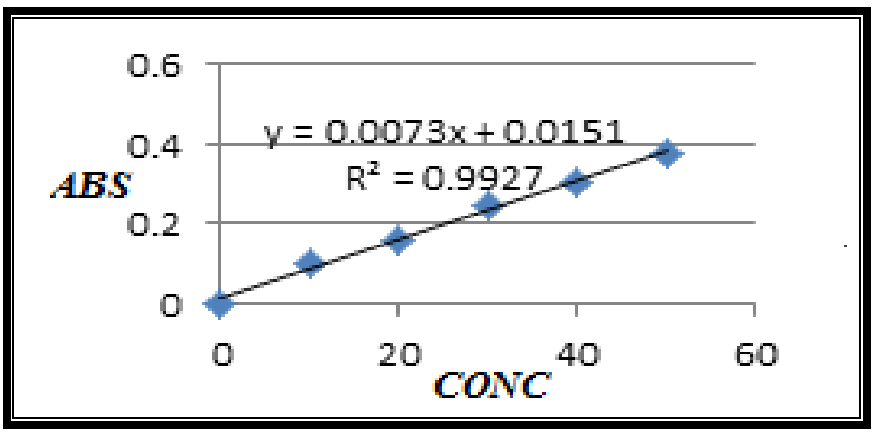

Figure 4: Calibration Curve KETOPROFEN

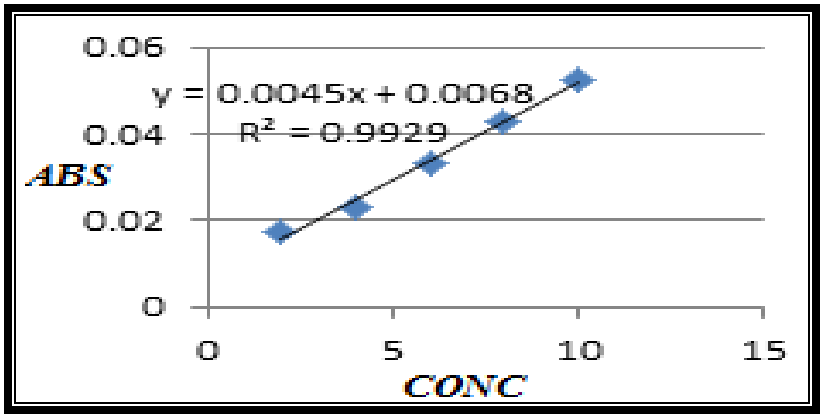

Figure 5: Calibration Curve METHYL PARABEN

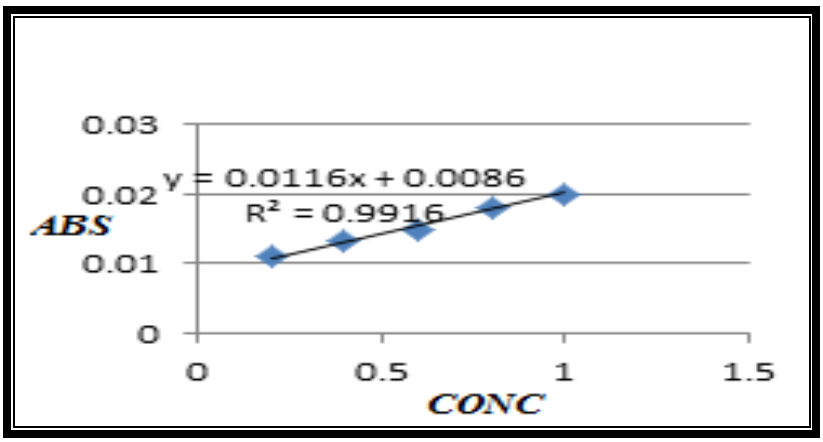

Figure 6: Calibration Curve PROPYL PARABEN

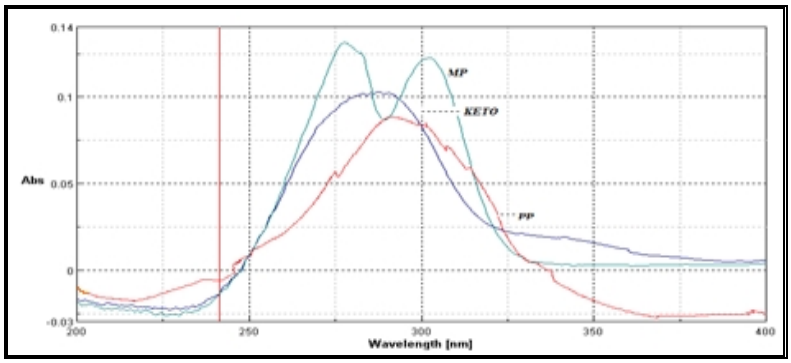

Figure 7: Overlain Spectra of KETO, MP, PP for Simultaneous Method

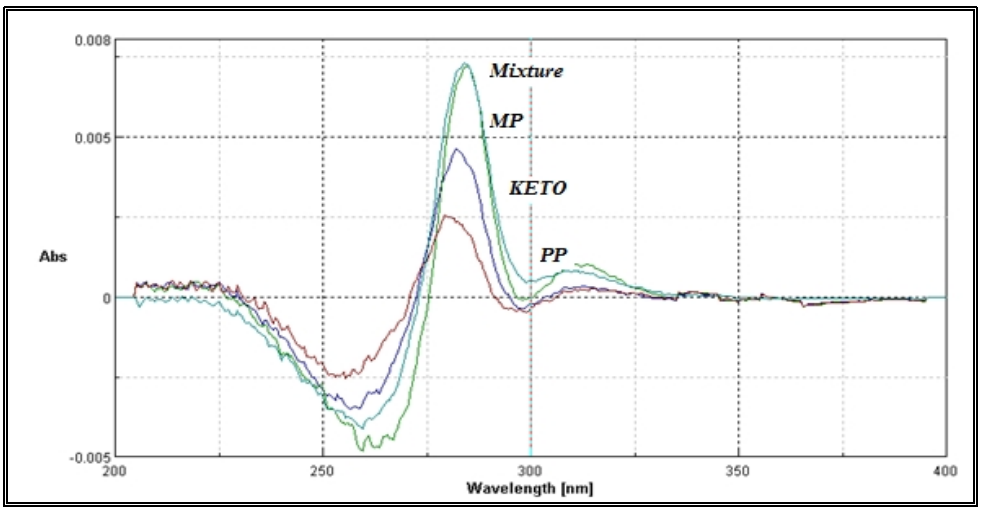

Figure 8: Overlain Spectra of KETO, MP, PP for First Order Derivative

RESULTS AND DISCUSSION

In the present work, new method, namely, simultaneous equation method (Vierordt's method) was used for the simultaneous spectroscopic estimation of KETO, MP and PP in commercially available Gel dosage form. The concentrations in the range of 2-20 µg/mL of mixed working standard and three sampling wavelengths of 288 nm (λ max of KETO), 308 nm (λ max of MP) and 309 nm (λ max of PP) for both method. The first derivative method was based on derivative spectrophotometric method and absorbance nm, which was the wavelength used (Figure 8). The calibration curves were constructed in the range of expected concentrations (10-50 ug/ml for Ketoprofen and 2-10 ug/ml for Methyl Paraben (MP), 0.2-1.0 ug/ml for Propyl Paraben, (PP). The representative equation analysis was Y= 0.0073x + 0.0151, Y = 0.0453x + 0.0068, Y = 0.0116x + 0.0086 with a correlation coefficient of 0.9999 for both methods (Table 6, 7 and 8). LOD and were found to be 0.022, 0.011, µg/mL for KETO and 0.031, 0.020 µg/mL for MP, 0.010, 0.013 for PP LOQ were found 0.033, 0.020, µg/mL for KETO and 0.010, 0.021 µg/mL for MP, 0.009, 0.011 for PP respectively. The experimental values obtained for the determination of KETO, MP and PP in the samples indicated a satisfactory intra-day validaty and inter-day variability (SD of 0.011, 0.1058 and 0.023, 0.049 for method I and Method II for KETO, SD of 0.0108, 0.116 and 0.0211, 0.130 for method I and Method II for MP and SD of 0.0115, 0.114 and 0.102, 0.117 for method I and Method II for PP. A good accuracy of the method was verified with a mean recovery of 100.70 and 10086 method I and method II for KETO and 100.29 and 100.66 method I and method II for MP and 99.98 and 99.56 method I and method II for PP (Table 6, 7 and 8).

CONCLUSION

The proposed method for simultaneous estimation Method I and Method II of Ketoprofen, Methyl Paraben and Propyl Paraben in their combined dosage and validated as per ICH guidelines. Moreover the method is economic, simple and rapid, hence can be employed for routine analysis in quality control laboratories

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