DISSOLUTION METHOD DEVELOPMENT AND VALIDATION FOR COMBINATION OF IBUPROFEN AND PARACETAMOL TABLETS

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ABSTRACT

The aim of this investigation was to develop and validate a dissolution method for combination of ibuprofen and paracetamol tablets using UV spectrophotometric method. The analytical method was developed by UV spectrophotometry using absorbance ratio method which involves the measurement of absorbance at two wavelengths 243 nm as the λ_{max} of ibuprofen and 213.8 as isoabsorbtive point. The method was validated according to ICH guidelines which include accuracy, precision, specificity, linearity and analytical range. In addition, stability and solubility of both the drugs in different media i.e., water and phosphate buffer of different pH were studied. Based on this, the established dissolution conditions were 900 ml of 0. 2 M phosphate buffer pH 7.2 as dissolution medium at 37±0.5 °C, using USP apparatus II at a stirring rate of 75 rpm for 1 hr. The corresponding dissolution profiles were constructed and all the selected brands showed more than 80% drug release within 45 minutes. Thus, the proposed dissolution method and analytical method can be applied successfully for the Quality control of ibuprofen and paracetamol in marketed tablets.

Keywords: Dissolution, Ibuprofen, ICH guidelines, Paracetamol, UV Spectrophotometric method.

INTRODUCTION

The dissolution test is a simple and useful *in vitro* tool that can provide valuable information about drug release similarity among different batches and brands. It describes about manufacturing reproducibility, product performance similarity and biological availability of drug from its formulation. Therefore, it is considered as one of the most important quality control parameter for solid pharmaceutical dosage forms. [1]

Chemically Ibuprofen (IBU) is 2-[4-(2-methylpropyl) phenyl] propanoic acid (as shown in figure 1). Ibuprofen is a Non-steroidal anti-inflammatory drug (NSAID). [2] Chemically, Paracetamol (PCM) is N-(4-hydroxyphenyl) ethanamide (as shown in figure 2). It is widely used as analgesic and anti-pyretic. [3]

Both the drugs are available in combined tablet dosage form, as an NSAID's. The extensive literature survey revealed that numbers of methods are reported for the individual drugs and combinations using UV, HPLC [4, 5, 6] (Riddhi G*et al*; Rupali S. J *et al*, Narasimha S. L *et at.*) but no method is so far reported for the simultaneous estimation of both drugs in combined dosage forms. Aim of the present work is to develop simple, precise, accurate, linear and specific method for simultaneous determination of Ibuprofen and Paracetamol in tablet dosage form and application of the method for the dissolution study. The method was validated according to the *International Conference on Harmonisation* guidelines (ICH Q2 R1).

This paper describes the method for simultaneous determination of Ibuprofen and Paracetamol drugs in dissolution test of tablets. The procedure is based on the use of UV Spectrophotometric multicomponent analysis i.e.; Absorbance ratio method.
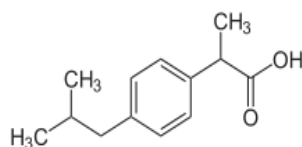

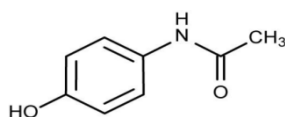**FIGURE 1: CHEMICAL STRUCTURE OF IBUPROFEN**

FIGURE 2: CHEMICAL STRUCTURE OF PARACETAMOL

MATERIALS AND METHODS

Materials

Ibuprofen and Paracetamol was received as a gift samples from Aurobindo Pharmaceuticals Ltd. (Hyderabad, India). Potassium dihydrogen orthophosphate and Sodium hydroxide pellets were procured by SD Fine Chem LTD. (Mumbai). All reagents and solvents used were of analytical grade.

Methods

UV Method Development and Validation

Determination of λ_{max}:

An accurately weighed quantity of PCM and IBU (10 mg) each were transferred in 100 ml volumetric flask, dissolved in sufficient quantity of phosphate buffer pH 7.2. The volume was made up to the mark with phosphate buffer pH 7.2 to get the concentration 100 µg/ml. An aliquot (1 ml) of this solution was diluted with phosphate buffer pH 7.2 in a 10 ml volumetric flask up to mark to get final concentration 10 µg/ml. The standard solution of PCM and IBU were scanned in the range of 200-400 nm in 1.0 cm cell against phosphate buffer pH 7.2 using UV spectrophotometer (Shimadzu, Japan) and spectra was recorded to determine the λ_{max} of both the drugs. Figure 3 shows the overlain spectra of PCM and IBU drugs.
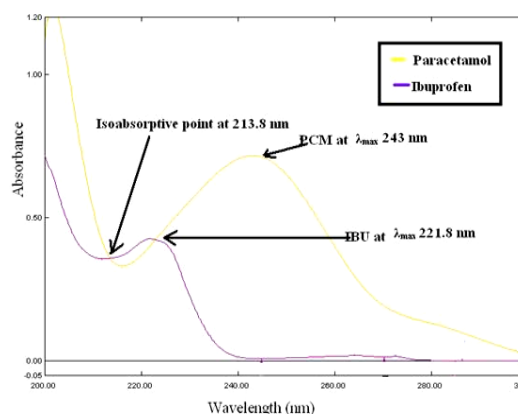

FIGURE 3: OVERLAIN SPECTRA OF PCM AND IBU

Preparation of standard solutions and Calibration curve

From the stock solution of PCM and IBU (100 μg/ml), sample solutions of PCM were prepared in the concentration range of 2 μg/ml to 14 μg/ml and 2 μg/ml to 20 μg/m for IBU by transferring appropriate volume to 10 ml of volumetric flask and making up the volume with phosphate buffer pH 7.2. All dilutions were scanned in wavelength range of 200 nm to 400 nm. The absorbance was plotted against the respective concentrations to obtain the calibration curve of both the drugs. The UV spectra for the linearity of both the drugs are shown in Figure 4 and 5. The calibration curves of both the drugs are shown in Figure 6.
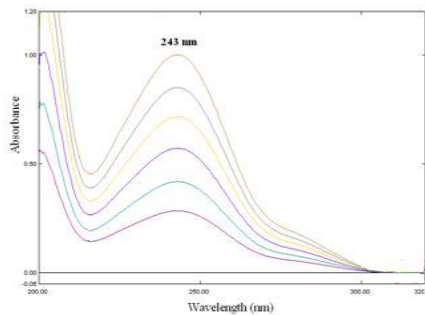
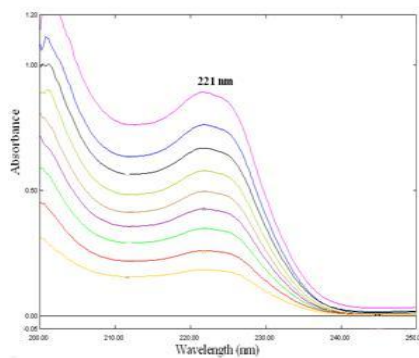

FIGURE 4: UV SPECTRA FOR THE LINEARITY OF PCM

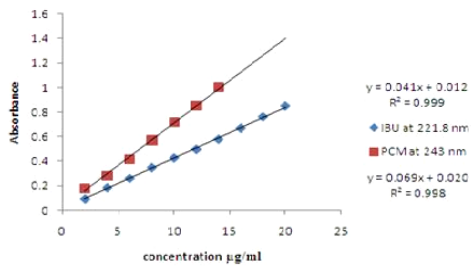**FIGURE 5: UV SPECTRA FOR THE LINEARITY OF IBU**

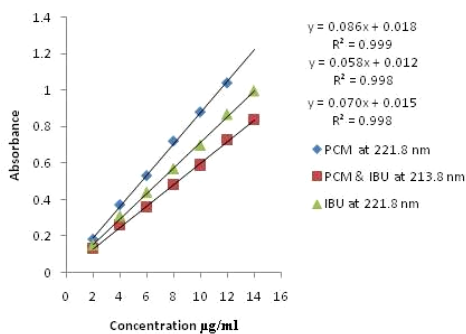**FIGURE 6: CALIBRATION CURVE OF PCM AND IBU PURE DRUG.**

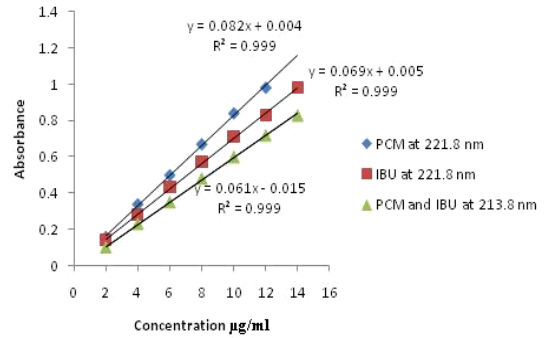**FIGURE 7: LINEARITY CURVE OF PCM AND IBU IN COMBIFLAM**

FIGURE 8: LINEARITY CURVE OF PCM AND IBU IN IBUGESIC PLUS

Determination of Absorpitivity value

The absorbance of each of the final dilution (10 μg/ml PCM and10 μg/ml IBU) was measured in triplicate in 1.0 cm cell against phosphate buffer pH 7.2 at 221.8 and 213.8 nm and A(1% 1cm) values were calculated using below formula.[7]

$$\text{Absorpitivity A (1\%, 1 cm)} = \frac{\text{Absorbance at selected wavelengths}}{\text{gm / 100 mL (conc)}} \times 100$$

Absorbance ratio method

Absorbance ratio method of analysis is based on the absorbance at two selected wavelengths, one of which is an absorptive point and the other being the wavelength maximum absorption of one drug. From the overlain spectra (Figure 3), 221.8 nm (λ_{max} of IBU) and 213.8 nm (isoabsorptive point) are selected for the formation of absorbance (Q) (Equation 1 and Equation 2). The Absorpitivity values determined for the PCM are 352 (ax 1), 351.2 (ax 2) and for IBU are 432.45 (ay 1), 351.2 (ay 2) at 221.8 nm and 213.8 nm respectively. These values are means of six estimations. The absorbance and absorptivity at these wavelengths were substituted in equation 1 and 2 to obtain the concentration of drugs. [8]

$$Cx = \frac{Qm - Qy}{Qx - Qy} \times \frac{A}{ax1} \qquad \text{------------------Eq 1}$$

$$Cy = \frac{Qm - Qx}{Qy - Qx} \times \frac{A}{ay1} \qquad \text{------------------Eq 2}$$

Where,

C_X= Concentration of Paracetamol.

C_Y= Concentration of Ibuprofen.

A= Absorbance of mixture at isoabsorptive point.

Q_M= Ratio of absorbance of laboratory mixture at 221.8 nm and 213.8 nm.

Q_X= Ratio of absorptivity of Paracetamol at 221.8 nm and 213.8 nm.

Q_Y= Ratio of absorptivity of Ibuprofen at 221.8 nm and 213.8 nm.

Estimation of PCM and IBU in Marketed tablets

For the estimation of PCM and IBU in commercial formulation, twenty tablets of each brand-COMBIFLAM (Aventis) and IBUGESIC PLUS (Okasa) containing 325 mg PCM and 400 mg IBU were weighed accurately and ground to a fine powder. A quantity equivalent to 22 mg of PCM was transferred to a 100 ml volumetric flask. IBU present in this tablet powder was 27 mg. The powder was dissolved in suitable quantity of phosphate buffer pH 7.2 with vigorous shaking and sonicated for 10 min and volume was made up to the mark. The sample solution was then filtered through Whatmann filter paper. The solution was further diluted to get final concentration of 2 μg/ml to 14 μg/ml of PCM and 2 μg/ml to

20μg/ml of IBU. Absorbances of each of the resulting solution were measured at 213.8 and 221.8 nm in 1.0 cm cell using phosphate buffer pH 7.2.

Validation Parameters

Validation of the proposed methods was carried out for its linearity & Range, Accuracy, Specificity and Precision according to ICH guidelines. [9]

Linearity and Range

For the determination of linearity, sample solutions of different concentrations were prepared for PCM and IBU. The absorbance of the above solutions was measured at 243 nm and 213.8 nm respectively for PCM and IBU. A graph of absorbance vs. concentration is plotted and correlation coefficient was calculated. The linearity data of the both drugs for two brands are presented in Table 1. The linearity curves are depicted in Figure 5 & 6 for both the drugs.

Accuracy

To check the accuracy of the proposed method, recovery studies were carried out at 50, 100 and 150% of the test concentration as per ICH guidelines for both the drugs. The recovery study was performed in triplicate at each level. The result of the recovery studies for the two brands is reported in Table 2 and Table 3.

The absorbance of the standard solutions of 50%, 100% and 150% at 243 nm and 221.8 nm for PCM and IBU respectively were measured. From this, individual recovery and mean recovery values were calculated.

Precision

The precision was determined by studying the intermediate precision and repeatability. The percentage relative standard deviation (%RSD) was calculated.

Repeatability

To check the degree of repeatability of the methods, suitable sample solutions were prepared and statistical evaluation was carried out. Repeatability was performed for six times with tablets formulation. Data is presented in Table 4.

DISSOLUTION METHOD DEVELOPMENT

The best dissolution medium was selected on basis of the solubility studies. Various dissolution conditions were tested for the development of a suitable dissolution method for the dissolution study of PCM and IBU tablets. The following parameters were finalized:

Medium   :   0.2 M Potassium buffer pH 7.2

Volume   :   900 ml

Apparatus   :   USP type-II (Paddle)

rpm   :   75

Temperature :   37 ºC ± 0.5 ºC

Time Point   : Within 45 min the drug release is more than 85%

Preparation of test solution

A tablet was dropped into each of the six dissolution vessels of the Dissolution Apparatus USP type II (Tablet dissolution tester, USP

model: TDT-06P, Electrolabs, India) containing preheated dissolution medium to 37 ºC, 0.2 M phosphate buffer pH 7.2 after

testing the sink conditions. A 5 ml aliquot of the sample was withdrawn at 5, 10, 20, 30,45, and 60 min intervals replacing 5ml of dissolution medium each time.

Analysis of the dissolution sample

The diluted samples of dissolution were analyzed UV spectrophotometrically by the developed UV method and percentage drug release was calculated. The graph of percentage drug release verses time is shown in Figure 9.
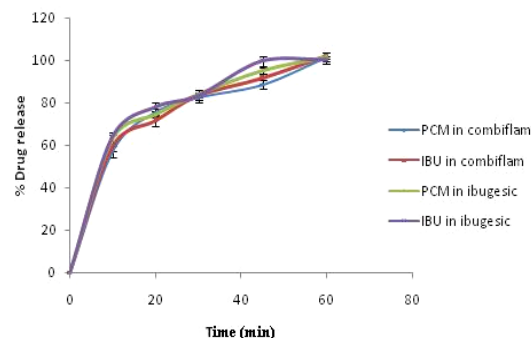

FIGURE 9: DISSOLUTION PROFILES OF PCM AND IBU IN MARKETED TABLETS.

RESULTS AND DISCUSSION

Determination of λ$_{max}$

The UV spectra for the linearity of both the drugs (PCM & IBU) are shown in Figure 4 and 5.

Beer's law is obeyed in concentration range of 2 to 14 μg/ml for PCM and 2 to 20 μg/ml for IBU.

Calibration curve of PCM and IBU pure drug is shown in figure 6.

Linearity and Range

The values of linearity of PCM & IBU in marketed tablets are shown in Table 1.

Linearity curve of PCM and IBU in Combiflam is shown in figure 7.

Accuracy

The results of recovery studies of Combiflam and Ibugesic Plus are shown in Table 2 and 3.

Precision

The results for repeatability are shown in Table 4.

The low %RSD values indicate that the method is precise.

DISSOLUTION METHOD DEVELOPMENT

The dissolution of PCM and IBU tablets was carried out in 900 ml of 0.2 M Phosphate buffer pH 7.2 maintained at 37 ºC ± 0.5 ºC, in paddle apparatus at 50 rpm and 75 rpm for 60 min. The diluted samples of dissolution were analyzed UV spectrophotometrically and % drug release is calculated and shown in Table. The graph of % drug release verses time is shown in Figure 8. The dissolution profile of PCM and IBU at 50 rpm and 75 rpm was performed and % drug release at 50 rpm was less than 85% release. So, 75 rpm is set as the dissolution rate for PCM and IBU tablets.

TABLE 1: RESULTS FOR LINEARITY READING OF PCM & IBU IN MARKETED TABLETS

Concentration (μg/ml)	Combiflam				Ibugesic Plus			
	PCM		IBU		PCM		IBU	
	221.8 nm	213.8 nm	221.8 nm	213.8 nm	221.8 nm	213.8 nm	221.8 nm	213.8 nm

2	0.18	0.15	0.15	0.13	0.16	0.10	0.12	0.10
4	0.37	0.31	0.31	0.26	0.34	0.23	0.28	0.23
6	0.53	0.44	0.44	0.36	0.50	0.35	0.42	0.35
8	0.72	0.60	0.57	0.48	0.67	0.48	0.57	0.48
10	0.88	0.78	0.70	0.59	0.84	0.60	0.71	0.60
12	1.04	0.91	0.87	0.73	0.98	0.72	0.86	0.72
14	1.23	1.04	1.00	0.84	1.176	0.83	0.99	0.83

TABLE 2: RESULTS OF RECOVERY STUDIES OF COMBIFLAM

% Conc at specific Levels	Paracetamol				Ibuprofen			
	Amount added (mg)	Amount recovered (mg)	% recovery	Mean recovery ± SD	Amount added (mg)	Amount recovered (mg)	% recovery	Mean recovery ± SD
50%	25	25.33	101.32	101.45 ± 0.150	5	4.95	99.0	99.13 ± 0.188
	25	25.39	101.58		5	4.962	99.25	
	25	25.36	101.46		5	4.957	99.15	
100%	50	50.86	101.73	101.83 ± 0.159	10	9.901	99.01	99.21 ± 0.166
	50	50.96	101.92		10	9.934	99.34	
	50	50.92	101.85		10	9.928	99.28	
150%	75	76.43	101.91	101.81 ± 0.179	15	14.88	99.12	99.24 ± 0.152
	75	76.37	101.83		15	14.89	99.27	
	75	76.26	101.69		15	14.90	99.35	

TABLE 3: RESULTS OF RECOVERY STUDIES OF IBUGESIC PLUS

% Conc at specific Levels	Paracetamol				Ibuprofen			
	Amount added (mg)	Amount recovered (mg)	% recovery	Mean recovery± SD	Amount added (mg)	Amount recovered (mg)	% recovery	Mean recovery ± SD
50%	25	24.88	99.52	99.74 ± 0.162	5	5.021	100.42	99.08 ± 0.141
	25	24.92	99.68		5	4.958	99.16	
	25	25.01	100.04		5	4.991	99.82	
100%	50	49.786	99.57	99.58 ± 0.116	10	9.973	99.73	98.96 ± 0.189
	50	49.899	99.79		10	9.959	99.59	
	50	49.9691	99.38		10	9.952	99.52	
150%	75	74.21	98.94	98.93 ± 0.115	15	14.852	99.01	99.79 ± 0.191
	75	74.56	99.41		15	14.845	99.96	
	75	73.84	98.45		15	14.839	99.92	

TABLE 4: RESULTS FOR REPEATABILITY

Brand	Concentration prepared (µg/ml)	Paracetamol		Ibuprofen	
		Concentration* (µg/ml)	%RSD	Concentration* (µg/ml)	%RSD
Combiflam	2	1.94 ± 0.6	0.5	1.98 ± 0.7	0.5
	4	4.82 ± 0.8	0.5	4.93 ± 0.3	0.2
Ibugesic Plus	2	1.89 ± 0.5	0.3	1.92 ± 0.5	0.4
	4	4.52 ± 0.7	0.5	4.89 ± 0.4	0.3

*Average of three determinations

CONCLUSION

Dissolution method was developed and validated for IBU & PCM tablets using UV spectrophotometric method the method was validated according to ICH guidelines which include accuracy, precision, specificity, linearity, and analytical range. Stability and solubility of both the drugs in different media i.e., water and phosphate buffer pH 7.2 was studied. Dissolution conditions were 900 ml of 0.2 M phosphate buffer pH 7.2 as dissolution medium at 37±0.5 °C; using USP apparatus II at a stirring rate of 75 rpm for 1 hr. Thus, the proposed dissolution method and analytical method can be applied successfully for the Quality control of IBU and PCM in marketed tablets.

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