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Original Article

Solid dispersion and air suspension techniques for obtaining controlled drug delivery system containing ketorolac and paracetamol

El-Gizawy S. A, Zein El Din E. E, Sherin Hammad• and Yassin H. A

Pharm. Technology and Analytical chemistry Dept•, Faculty of Pharmacy, Tanta University, Tanta, Egypt

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ABSTRACT

The present study reports on the formulation of ketorolac tromethamine loaded Eudragit RS100, Eudragit RL100 as well as Ethyl cellulose as a controlled release drug delivery system. Solid dispersion and microencapsulation by air suspension method were the techniques for choice. Paracetamol was added to the prepared formulations in the form of physical mixture in order to make use of the synergistic effect of the drug with different non-steroidal anti-inflammatory drugs (NSAIDs).

Keywords: Ketorolac and paracetamol synergistic effect, First derivative spectrophotometric assay, of ketorolac and paracetamed, ketorolac delivery system, ketorolac solid dispersion technique.

INTRODUCTION

Ketorolac is a non-steroidal anti-inflammatory agent with significant analgesic effects **(1)**. It acts primarily by decreasing the synthesis and release of prostaglandins, which are responsible for enhancing the pain response to chemical mediators and mechanical stimuli **(2)**. Several studies **(3-5)** suggest that ketorolac is comparable to opioids when used to treat acute pain. Paracetamol has antipyretic and analgesic potential similar to NSAIDs; however, it is different from NSAIDs; it lacks anti-inflammatory, antiplatelet and gastrotoxic activities **(6, 7)**. Paracetamol is often combined with NSAIDs in the management of acute and chronic pain **(6)**. Paracetamol exerts its action by inhibition of prostaglandin synthesis. Several clinical studies **(8, 9)** have failed to show a reduction in peripheral prostaglandins in response to paracetamol. The drug is only a weak inhibitor of peripheral prostaglandin synthesis **(9)**. It was proposed that paracetamol exerted its analgesic action by inhibition of centrally situated isoform of cyclooxygenase enzymes **(10)**.

Co-administration of combination of paracetamol with NSAIDs diclofenac, ibuprofen, ketoprofen, meloxicam, naproxen and nimesulide was studied by iso-bolographic analysis. The effective dose that produced 50% anti-nociception was calculated **(11-13)**. As shown by iso-bolographic analysis, all combinations were synergistic. The studies demonstrated potent interactions between paracetamol and NSAIDs and showed validation of the clinical use of combination of the tested drugs in the treatment of pain condition. The rationale underlying the practice of combining drugs in pain management is based mainly on the consideration that combing drugs that act at different pain mechanisms may enhance pain relief. NSAIDs block peripheral biosynthesis of prostaglandins by inhibiting the COX enzymes, whereas paracetamol act mainly on the brain and spinal cord; nevertheless, the exact mechanism of action of the later is still unknown **(14)**.

The purpose of the present study was to make use of the synergistic effects reported between paracetamol and NSAIDs to obtain a combination of ketorolac tromethamine in the form of solid dispersion as well as microencapsulation drug delivery systems containing Eudragit RS100, Eudragit RL100, and ethyl cellulose with paracetamol in order to obtain a formula facilitating patient compliance and exerting antipyretic as well as anti-inflammatory activity, simplifying prescribing, improving efficacy with decreasing adverse effects aiming that their co-administration

***Corresponding Author Address:** Esmat Zein El Dein Pharm. Technology Dept., Faculty of Pharmacy, Tanta University, Tanta, Egypt*
E-mail: dr.esmat.zein@gmail.com

will result in decreasing the individual doses of each drug. Both drugs are simultaneously estimated using a unique analytical technique.

MATERIALS AND METHODS

Materials: Ketorolac tromethamine (Sigma-Aldrich, St. Louis, Mo, USA) was a gift sample kindly supplied by Amriya pharmaceuticals industries, Alexandria, Egypt , Paracetamol (Sigma- Aldrich, St. Louis, Mo, USA) was a gift sample kindly supplied by Sigma pharmaceuticals industries, Quesna, Egypt , Eudragit RS100 and Eudragit RL100 were purchased from RÖhm Pharma GMBH , Darmstadt (Germany) , Ethyl cellulose was obtained from Sigma- Aldrich Chemi (Germany) . All other reagents and chemicals were analytical grades and were used as received.

Preparation of solid dispersion: Three types of solid dispersion of ketorolac tromethamine with Eudragit RS100, Eudragit RL100 and Ethyl cellulose (in a ratios of 1:3) drug to polymer were prepared .The method was achieved by dissolving 1500 mg of the polymer in a mixture of ethanol: dichloro methane in a ratio of (1:1) in a glass vessel at 40^{o} C using Vortex Mixer (Maxi mix 11, Thermolyne Corporation, U.S.A.). The mixture was stirred at 400 rpm in a water bath (KOWELL N4, Germany) over 20 min. The mixture of ethanol: dichloro methane in a ratio of (1:1) was used as a solvent for the used polymers. 500 mg of drug was gradually added to the above mixture with stirring until completely dissolved. The rotation speed of the magnetic stirrer was continued until the solvent mixture was removed by evaporation. The dry film obtained was pulverized and passed through No 450µm sieve in order to obtain a homogenous particle size **(15-17)**. The obtained product was kept in a desiccator over silica gel under reduced pressure until used. Paracetamol was blended with the prepared solid dispersions in order to obtain a blend containing ketorolac tromethamine solid dispersions with paracetamol in a physical mixture form.

Coating of ketorolac tromethamine with Eudragit RS100, Eudragit RL 100 and ethyl cellulose:

Preparation of the coating solution: Coating solutions with concentration of 5% w/v Eudragit RS100, Eudragit RL100 or ethyl cellulose in acetone-isopropyl alcohol mixture (1:1) were prepared by dissolving 30gm of each Eudragit RS100, Eudragit RL 100 or ethyl cellulose separately in 200ml solvent mixture **(18,19)**.

***Coating technology*:** Reviewing the literature about air suspension technique revealed that microencapsulation by this technique reduces processing time and improves the product properties. It was also proven to be more convenient method especially in case of thermo-labile materials. The process consists simply of supporting 30gm drug in the vertical container simply fluidized from below by a stream of air. The exhaust filter was shaken from time to time to keep the entire drug inside the container. After adjusting the atomized compressed air, the solution of 5% w/v of either Eudragit or ethyl cellulose in acetone-isopropyl alcohol mixture (1:1) was sprayed over the bed. The spraying pump was adjusted to be 10 rpm to give a suitable droplet size from the sprayed solution. The temperature was maintained at 35-40^{o} C during the coating process. The volume of the solution needed to produce the desirable microcapsules was 200 ml. When the microcapsules have been formed, the spray was turned off and the product was left to fluidize inside the apparatus for about 60 minutes for complete drying at the same temperature. The same procedure was followed to obtain 1:2 and 1:3 drug to polymer ratios. The encapsulated particles were stored in a desiccator over anhydrous calcium chloride for 48hrs before any further study. Table 1 shows the operating condition in coating ketorolac tromethamine powder

Granulation of paracetamol: Wet granulation method was utilized for obtaining paracetamol granules so as to prevent segregation of the drug if added to ketorolac solid dispersion or ketorolac microcapsules. Paracetamol was kneaded with distilled water (quantity sufficient) and the wet mass was passed through No 450µm sieve in order to obtain a homogenous particle size. The granules were left to dry under ambient temperature. The obtained product was kept in a desiccator over silica gel under reduced pressure until used.

Determinations of ketorolac and paracetamol in the prepared blend: A derivative spectrophotometric method was developed. Since the zero-order spectra of the two drugs are overlapping, the determination of those ingredients using the conventional UV spectrophotometry has become invalid. Derivative spectrophotometry is an analytical technique of great utility for extracting both qualitative and quantitative information from spectra composed of unresolved bands. The derivative absorbance at certain chosen wavelengths allowed the concurrent determination of the two components without preliminary separation or extraction of any of them. The zero-crossing method is the most common procedure for conducting analytical calibration in derivative spectrophotometry **(20-23)**.

Instrumentation: UV and derivative spectra of the solutions were recorded on double beam UV–Vis spectrophotometer Shimadzu 1800 using 10 mm path length quartz cells, scan range of 200–500 nm, delta wavelength 5nm and scaling factor 1.

Preparation of standard solutions and construction of calibration curves:

For paracetamol: Stock standard solution of paracetamol was prepared in 0.1N HCl to give a final concentration of 1.0 $mg.ml^{-1}$. Different aliquots from this stock solution were taken and diluted with 0.1N HCl to obtain solutions of paracetamol in the concentration range (2-10 $\mu g.ml^{-1}$). The zero order absorption spectra were recorded against 0.1N HCl as a blank. The absolute values of the first order derivatives were obtained by zero-crossing technique. Calibration curves were constructed by plotting the values of the first derivative absorbance (^1D) at zero-crossing point for ketorolac 249 nm against corresponding concentrations of standard solutions. Similarly stock standard solution of paracetamol was prepared in phosphate buffer pH 7.4 to give a final concentration of $1mg.ml^{-1.}$ Different aliquots from this stock solution were taken and diluted with the buffer to obtain solutions of paracetamol in the concentration range (2-10 $\mu g.ml^{-1}$). The zero -order absorption spectra were recorded against phosphate buffer pH 7.4 as blank. Calibration curves were constructed by plotting the values of the first derivative absorbance (^1D) at 233 nm against corresponding concentrations of standard solutions.

For ketorolac tromethamine: Stock standard solution of ketorolac was prepared in distilled water to give a final concentration of $1mg.ml^{-1}$. Different aliquots from this stock solution were taken and diluted with 0.1N HCl to obtain solutions of Ketorolac in the concentration range (2-10 $\mu g.ml^{-1}$). The zero order absorption spectra were recorded against 0.1N HCl as a blank. Calibration curves were constructed by plotting the values of the first derivative absorbance (^1D) at 338 nm against corresponding concentrations of standard solutions. Similarly stock standard solution of ketorolac was prepared in phosphate buffer pH 7.4 to give a final concentration of $1mg.ml^{-1}$. Different aliquots from this stock solution were taken and diluted with the buffer to obtain solutions of ketorolac in the concentration range (2-10 $\mu g.ml^{-1}$). The zero order absorption spectra were recorded against phosphate buffer pH 7.4 as blank. Calibration curves were constructed by plotting the values of the first derivative absorbance (^1D) at 304 nm against corresponding concentrations of standard solutions.

In vitro **drug release studies:** The dissolution rate of ketorolac tromethamine solid dispersions equivalent to (10mg) and ketorolac tromethamine microcapsules as well as (500 mg) of paracetamol in a physical mixture form was studied using USP dissolution test apparatus employing paddle type (Paddle type, Copley, England). Each sample was placed in 900ml of the dissolution media, pH 1.2 (0.1 N HCL) and pH 7.4 (phosphate buffer). Paddle speed of 100 rpm and temperature of $37.5^oC \pm 0.2$ were employed. Aliquots (5ml) were withdrawn , filtered through 0.45 membrane filter at 5, 10, 15, 20, 30, 45, 60, 90 and 120 min and replaced with equal volumes of prewarmed fresh medium to maintain constant volume and keep sink condition. The drugs' concentration and the percentage drug released were determined spectrophoto-metrically with respect to time. Studies were performed in triplicate for each sample and the results were reported as mean ± SD.

Assay of the prepared blend:

Simultaneous determination of ketorolac and paracetamol: Five ml of dissolution media at predetermined time intervals was withdrawn and replaced with free media at the same temperature.

The zero order spectrum of this aliquot of dissolution medium was recorded against 0.1 N HCl (dissolution medium 1) or pH 7.4 (dissolution medium 2) as a blank. For dissolution medium (1): the ^1D value was recorded at 249 and at 338 for determination of paracetamol and ketorolac respectively then the concentration of each drug was calculated from the corresponding regression equation of its calibration curve. For dissolution medium (2): the ^1D value was recorded at 233 and at 304 for determination of paracetamol and ketorolac respectively, then the concentration of each drug was calculated from the corresponding regression equation of its calibration curve.

RESULTS AND DISCUSSION

The overlain of zero-order spectra, 1st order spectra in phosphate buffer (pH 7.4) and the overlain of zero-order spectra, 1st order spectra in 0.1N HCl (pH 1.2) are reported in fig. 1 and fig. 2.

Validation of the proposed first derivative spectrophotometric method: The Validity of the method was tested regarding linearity, specificity, accuracy, and precision according to ICH guide lines (ICH-Q2B, 2005) **(24).**

Linearity and range: The calibration graphs for the determination of ketorolac and paracetamol by the proposed method were constructed by plotting the derivative amplitudes versus the concentrations. The graphs were found to be rectilinear over the

concentration ranges cited in Table (2). Statistical analysis of the data gave high values of correlation coefficients of the regression equations, small values of the standard deviations of intercept (Sa), and of slope (Sb). These data proved the linearity of the calibration graphs and the agreement of the result with Beer's law.

Limit of Detection (LOD) and Limit of Quantitation (LOQ): The limit of detection (LOD) was determined by evaluating the lowest concentration of the analyte that can be readily detected, while the limit of quantitation (LOQ) was determined by establishing the lowest concentration that can be measured above which the calibration graph is nonlinear. The results are shown in Table (1). LOQ and LOD were calculated according to the following equations **(24)**.

LOQ = 10 Sa / b, LOD = 3.3 Ss / b

Where Sa is the standard deviation of the intercept of regression line, and b is the slope of the calibration curve.

Accuracy and precision: To prove the accuracy of the proposed methods several synthetic mixtures of paracetamol and ketorolac in the ratio 1:1 were analyzed. Statistical analysis of the results involving the mean percent recoveries of both drugs in these mixtures are summarized in Tables 3 and 4. Intraday (repeatability) and inter-day (intermediate) precisions were assessed using three concentrations and three replicates of each concentration. The standard deviations were found to be very small indicating good repeatability over the entire concentration range, which revealed the precision of the proposed method as shown in Table 4.

***In- vitro* drug release from solid dispersion systems:** The release profile of ketorolac tromethamine solid dispersions prepared from different types of polymers (Eudragit RS100, Eudragit RL100 and ethyl cellulose) as well as the dissolution of paracetamol present as a physical mixture are presented in table 5 and 6 (pH 1.2 and pH 7.4) respectively. It is clear from table (5) that the percentage of ketorolac released from the solid dispersions over the experimental time period (120 min) were 17.50 ± 0.31, 31.28 ± 0.43 and 27.92 ± 0.35 from Eudragit RS100, Eudragit RL100 and ethyl cellulose respectively. The percentage of paracetamol dissolved from the physical mixture contained with solid dispersions were 97.41 ± 0.27, 94.50 ± 0.87 and 94.73 ± 0.41 respectively. From table (6), it is obvious that at pH 7.4 a controlled process of ketorolac percentage release from the solid dispersions and the subsequent dissolution began by 50.60 ± 0.22, 52.63 ± 0.75 and 58.63 ± 0.42 from Eudragit RS100, Eudragit RL100 and ethyl cellulose respectively after 5min. After 120 min the percentages were 70.16 ± 0.42, 71.83 ± 0.55 and 90.46 ± 0.51 respectively, this means that a controlled drug release all over the experimental time is obtained.

From table 5 and 6, it is clear that over 80% of ketorolac tromethamine is available to be released and absorbed from the intestine under the effect of the polymers chosen for the solid dispersion. These results can describe the effect of the solid dispersion technique in reducing to a great extent the ulcerogenic activity as well as the other gastrotoxic side effects of the drug.

***In- vitro* drug release from microcapsules systems:** The release profile of ketorolac tromethamine microcapsules systems prepared from different types of polymers (Eudragit RS100, Eudragit RL100 and ethyl cellulose) as well as the dissolution of paracetamol present as a physical mixture are presented in table 7 and 8 (pH 1.2 and pH 7.4) respectively**.** It is clear from table (7) that the percentage of ketorolac released from the microcapsules over the experimental time period (120 min) were 14.39 ± 0.28, 17.15 ± 0.48and 13.12 ± 0.86 from Eudragit RS100, Eudragit RL100 and ethyl cellulose respectively. The percentage of paracetamol dissolved from the physical mixture contained with microcapsules were 97.55± 0.30, 94.34 ± 1.78 and 95.23 ± 0.21 respectively. From table (8), it is obvious that at pH 7.4 a controlled process of ketorolac percentage release from the microcapsules and the subsequent dissolution began by 37.15 ± 1.03, 20.98 ± 0.54and 15.34 ±0.52from Eudragit RS100, Eudragit RL100 and ethyl cellulose respectively after 5min. After 120 min the percentages were 52.75 ± 0.98, 52.56 ± 1.11and 55.11± 1.71 respectively, this means that a controlled drug release all over the experimental time is obtained. From table 7 and 8, it is clear that over 55% of ketorolac tromethamine is available to be released and absorbed from the intestine under the effect of the polymers chosen for the microcapsules.

The observed dissolution behavior of both drugs may give an answer on the exact mechanism of the synergistic action of paracetamol on different anti-inflammatory drugs where paracetamol rapidly dissolves at the acidic gastric pH followed by its absorption in the stomach exerting its effect on the brain and spinal cord **(6)** accompanied by gradually increasing amounts of ketorolac which acts by blocking the peripheral biosynthesis of prostaglandins by inhibiting the cyclooxygenase enzyme. At the same time, paracetamol lacks the

antiplatelet and gastro-toxic activities **(13)**. The speed of release and absorption in addition to the high bioavailability of paracetamol (63-89%), also the drug is not subjected to a large degree of first-pass metabolism in the liver **(23)**. All these postulations can describe the importance of the practice of combining both drugs in one formulation. These results are in agreement of the studies which performed and showed the effect of such combination on increasing the analgesic effect and pain relief which necessitated the reduction of the anti-inflammatory dose by 37% - 46% **(25-28)**.

These results can describe the effect of the microencapsulation technique in reducing to a great extent the ulcerogenic activity as well as the other gastro-toxic side effects of the drug. In a previous study in our laboratory the authors proved that there is no interaction between ketorolac tromethamine and the polymers used in this study **(29)**.

CONCLUSION

From the previous result, it is clear that microencapsulation technique is better than solid dispersion technique in coating efficiency as well as in drug release. Microencapsulation technique has a great role in reducing the ulcerogenic as well as the other gastro-toxic side effects of ketorolac tromethamine. Co-administration of combination of paracetamol with ketorolac tromethamine showed synergistic effects leading to validation of clinical use of this combination in the treatment of majority of pain conditions.

Table (1): Operating Condition in Coating Ketorolac Tromethamine Powder:

Operating Condition in Coating Ketorolac Tromethamine Powder	
Core material	**Ketorolac**
Inlet air temperature (^{o}C)	(60**)**
Material temperature (^{o}C)	(35-40**)**
Out let air temperature (^{o}C)	(33-36)
Air flow rate (m^3 / min.)	(0.75-0.9)
Spray rate (ml / min.)	(6.9)
Spray pressure (atm.)	(1.5-2.0)
Diameter of spray nozzle (mm)	(0.8)
Drying conditions	(40^{o}C, 60min)
Mesh size	(80-250)
Charged weight (gm.)	(30)

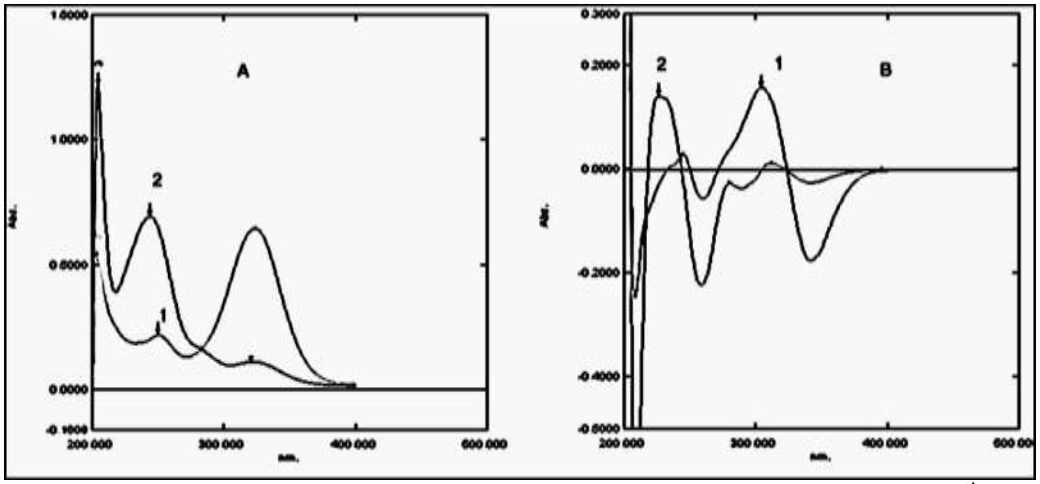

Fig.(1) Overlain of zero-order spectra (A) for ketorolac (1)& paracetamol (2) and 1st order spectra(B)for ketorolac(1) & paracetamol (2) in phosphate buffer (pH 7.4).

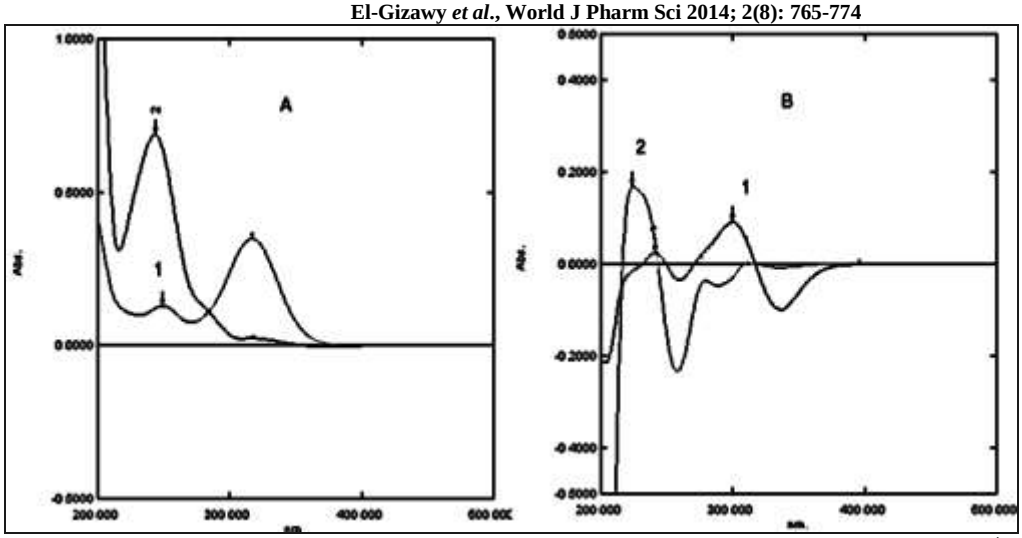

Fig. (2) Overlain of zero-order spectra (A) for ketorolac (1) & paracetamol (2) and 1st order spectra (B) for ketorolac (1) & paracetamol (2) in 0.1N HCl (pH 1.2).

Table 2: Statistical data of calibration curves of ketorolac tromethamine and paracetamol by the proposed first derivative spectrophotometric method:

Parameter	In pH 1.2		In pH 7.4	
	Ketorolac	Paracetamol	Ketorolac	Paracetamol
Linearity Range,µg.ml^{-1}	2-10	2-10	2-10	3-10
Regression equation	$^{1}D_{338}$=0.014x	$^{1}D_{249}$= 0.012x+0.02	$^{1}D_{304}$= 0.015x+0.002	$^{1}D_{233}$= 0.016x-0.038
Correlation coefficient	0.99990	0.9990	0.9990	0.9990
SD about slope	0.000003	0.00019	0.0014	0.0003
SD about intercept	0.00020	0.001200	0.0002	0.00205
LOD, µg.ml^{-1}	0.30000	0.31000	0.3000	0.4000
LOQ, µg.ml^{-1}	0.9000	1.9500	0.9000	1.2300

Table (3) Recovery of synthetic mixtures of ketorolac tromethamine and paracetamol by the proposed method:

drug	Concentration taken, µg.ml^{-1}	Mean* % recovery	
		In pH 1.2	In pH 7.4
ketorolac	2.0	99.00 ± 0.04	102.00 ± 0.02
	7.0	99.10 ± 0.10	99.57 ± 0.02
	9.0	100.40 ± 0.05	100.20 ± 0.03
paracetamol	2.0	100.50 ± 0.01	99.50 ± 0.02
	7.0	99.85 ± 0.03	100.14 ± 0.02
	9.0	99.77 ± 0.02	99.88 ± 0.03

***average of three determinations ± S.D.**

Table (4): Precision data for the determination of ketorolac tromethamine and paracetamol in mixtures of both by the proposed method:

drug	Concentration used, µg.ml^{-1}	Intra-day *		Inter-day *	
		Concentration found µg.ml^{-1}		Concentration found µg.ml^{-1}	
		In pH 1.2	In pH 7.4	In pH 1.2	In pH 7.4
ketorolac	2.0	1.99 ± 0.04	1.99 ± 0.04	1.99 ± 0.04	1.96 ± 0.02
	7.0	7.02 ± 0.10	7.00 ± 0.04	6.99 ± 0.08	6.99 ± 0.02
	9.0	8.99 ± 0.05	8.99 ± 0.02	9.03 ± 0.04	9.01 ± 0.03
paracetamol	2.0	1.99 ± 0.01	2.00 ± 0.02	1.98 ± 0.01	1.99 ± 0.02
	7.0	6.98 ± 0.03	6.99 ± 0.02	6.99 ± 0.03	6.99 ± 0.01
	9.0	9.01 ± 0.02	8.99 ± 0.03	8.99 ± 0.03	8.99 ± 0.03

***average of three determinations ± S.D.**

Table (5): Simultaneous dissolution of ketorolac tromethamine solid dispersion in combination of paracetamol physical mixture at pH 1.2:

Time (min) / Drug	% Drug Dissolved *		
	Polymer used in Solid Dispersion		
	Eudragit RS 100	Eudragit RL 100	Ethyl Cellulose
5 a	3.18 ± 0.43	2.71 ± 0.98	3.07 ± 0.45
5 b	69.66 ± 0.90	69.16 ± 0.77	77.83 ± 0.18
10 a	3.50 ± 0.87	3.42 ± 0.65	3.78 ± 0.19
10 b	73.41 ± 0.73	74.33 ± 0.59	81.66 ± 0.54
15 a	4.00 ± 0.19	3.92 ± 0.34	5.14 ± 0.76
15 b	77.08 ± 0.94	77.33 ± 0.52	85.00 ± 0.06
20 a	4.20 ± 0.54	5.64 ± 0.09	5.96 ± 0.32
20 b	80.33 ± 0.21	79.91 ± 0.41	87.33 ± 0.64
30 a	4.82 ± 0.42	16.21 ± 0.15	8.07 ± 0.08
30 b	81.00 ± 0.63	81.33 ± 0.70	88.66 ± 0.32
45 a	5.70 ± 0.93	19.92 ± 0.28	11.71 ± 0.39
45 b	84.83 ± 0.11	85.00 ± 0.15	89.33 ± 0.91
60 a	6.20 ± 0.22	25.14 ± 0.54	13.78 ± 0.64
60 b	88.25 ± 0.68	89.16 ± 0.23	90.16 ± 0.55
90 a	8.50 ± 0.88	28.71 ± 0. 87	16.57 ± 0.46
90 b	92.58 ± 0.44	93.41 ± 0.48	94.23 ± 0.33
120 a	17.50 ± 0.31	31.28 ± 0.43	27.92 ± 0.35
120 b	97.41 ± 0.27	94.50 ± 0.87	94.73 ± 0.41

a: ketorolac tromethamine b: paracetamol; The results are the mean of 3 readings ± SD.

Table (6): Simultaneous dissolution of ketorolac tromethamine solid dispersion in combination of paracetamol physical mixture at pH 7.4:

Time (min) Drug	% Drug Dissolved *		
	Polymer used in Solid Dispersion		
	Eudragit RS 100	Eudragit RL 100	Ethyl Cellulose
a b5	50.60 ± 0.22 90.11 ± 0.70	52.63 ± 0.75 90.42 ± 0.77	58.63 ± 0.42 90.29 ± 0.18
a 10 b	52.73 ± 0.78 92.41 ± 0.87	54.31 ± 0.42 92.18 ± 0.40	60.62 ± 0.13 92.14± 0.33
a 15 b	56.34 ± 0.17 93.16 ± 0.41	55.23 ± 0.60 93.91± 0.58	63.41 ± 0.35 94.31 ± 0.28
a 20 b	58.41± 0.74 95.13 ± 0.87	56.49 ± 0.43 95.21 ± 0.23	65.32 ± 0.28 95.41 ± 0.42
a 30 b	59.52 ± 0.32 96.02 ± 0.65	58.43 ± 0.08 96.53± 0.49	70.69 ± 0.17 97.32± 0.53
a b45	60.92 ± 0.98 96.83 ± 0.44	60.14 ± 0.87 97.12 ± 0.56	76.34 ± 0.21 98.13 ± 0.19
a b 60	62.44 ± 0.54 97.62 ± 0.77	65.34 ± 0.65 98.10 ± 0.16	80.31 ± 0.77 98.99 ± 0.42
a b 90	65.33 ± 0.23 99.26 ± 0.34	69.16± 0. 18 99.13 ± 0.10	84.52 ± 0.18 99.14 ± 0.30
a 120 b	70.16 ± 0.42 99.67 ± 0.80	71.83 ± 0.55 99.62 ± 0.81	90.46 ± 0.51 99.76 ± 0.15

a: ketorolac tromethamine b: paracetamol; The results are the mean of 3 readings ± SD.

Table (7): Simultaneous dissolution of ketorolac tromethamine microcapsules in combination of paracetamol physical mixture at pH 1.2:

Time (min) Drug	% Drug Dissolved *		
	Polymer used in microcapsules		
	Eudragit RS 100	Eudragit RL 100	Ethyl Cellulose
a b5	1.08 ± 0.87 69.62 ± 0.93	0.71 ± 0.52 69.56 ± 1.73	0.91 ± 0.20 77.32 ± 1.13
a 10 b	2.25 ± 0.14 73.41 ± 0.73	0.84 ± 0.26 74.53 ± 0.51	1.05 ± 0.12 81.43 ± 0. 64
a 15 b	2.89 ± 0.11 77.08 ± 0.94	3.23 ± 1.21 77.11± 0.12	1.16 ± 0.24 83.45 ± 1.09
a 20 b	4.19 ± 1.84 80.42 ± 0.52	4.82 ± 0.55 79.66 ± 0.88	2.16 ± 0.37 85.32 ± 0.04
a 30 b	5.30 ± 0.67 81.22 ± 0.46	6.52 ± 0.33 81.87± 0.36	3.19 ± 0.69 86.66 ± 1.23
a b45	6.14 ± 1.72 84.68± 0.18	12.48 ± 1.91 85.65± 0.19	5.21 ± 0.99 89.35 ± 0.41
a b 60	12.20 ± 0.23 88.31± 1.62	14.11 ± 1.32 89.98 ± 0.90	8.13± 0.81 91.10± 1.53
a b 90	13.07 ± 0.43 92.30 ± 1.42	16.22 ± 1.23 93.23 ± 1.98	10.45 ± 0.95 94.00 ± 1.32
a 120 b	14.39 ± 0.28 97.55± 0.30	17.15 ± 0.48 94.34 ± 1.78	13.12 ± 0.86 95.23 ± 0.21

a: ketorolac tromethamine b: paracetamol

Table (8): Simultaneous dissolution of ketorolac tromethamine microcapsules in combination of paracetamol physical mixture at pH 7.4:

Time (min) Drug	% Drug Dissolved *		
	Polymer used in microcapsules		
	Eudragit RS 100	Eudragit RL 100	Ethyl Cellulose
a b5	37.15 ± 1.03 90.18 ± 0.90	20.98 ± 0.54 90.11 ± 0.82	15.34 ± 0.52 90.21 ± 1.13
a 10 b	38.85 ± 1.29 93.61 ± 1.81	24.96 ± 0.64 91.19 ± 1.60	17.96± 1.34 92.17± 0.39
a 15 b	40.68 ± 0.20 94.00 ± 0.71	30.89± 1.32 94.21± 0.85	22.15 ± 0.18 94.51 ± 0.29
a 20 b	43.75 ± 0.38 95.25 ± 0.78	32.11 ± 0.48 94.99 ±1.12	25.97 ± 1.14 95.83 ± 1.40
a 30 b	45.00 ± 1. 26 96.19± 0.75	34.87 ± 0.76 97.14± 0.67	31.96 ± 0.32 97.28± 0.59
a b45	46.31 ± 1.13 96.71 ±1.40	37.98 ± 1.54 97.85± 0.26	45.98 ± 0.47 98.00 ± 0.91
a b 60	48.49 ± 0.90 97.81 ± 0.73	42.00 ± 0.29 98.80 ± 0.16	51.23 ± 1.32 98.83 ± 1.23
a b 90	50.25± 1.21 99.46 ± 0.84	48.94 ± 1.42 99.33 ± 1.10	53.87 ± 0.36 99.18 ± 0.34
a 120 b	52.75 ± 0.98 99.69 ± 0. 05	52.56 ± 1.11 99.82 ± 0.54	55.11± 1.71 99.98 ± 1.13

a: ketorolac tromethamine b: paracetamol; The results are the mean of 3 readings ± SD.

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