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AIR SUSPENSION AND SOLID DISPERSION TECHNIQUES FOR OBTAINING CONTROLLED DRUG DELIVERY SYSTEM CONTAINING KETOROLAC AND PANTOPRAZOLE

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) are important agents in the management of arthritic and inflammatory conditions, and are the most frequently prescribed medications. The present study reports on the formulation of ketorolac 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. One of the best choices to improve the GI safety is the co-medication of proton pump inhibitors (PPIs) with NSAID in one formula to suppress gastric acid. A fixed NSAID/PPI combination ensures expected protective effects by improving patients' PPI adherence and physicians' PPI prescription persistence. A fixed combination of enteric-coated ketorolac/pantoprazole formula has been studied. An accurate simple and précised method was adopted for simultaneous determination of ketorolac and pantoprazole in a physical mixture form. The method is based on measuring the first derivative amplitudes. The obtained results were validated for accuracy, precision, LOD, LOQ and were found to be satisfactory. The proposed method is simple, rapid and suitable for the assay of such combinations.

KEYWORDS: Solid dispersion, Microencapsulation, Controlled released systems, Combination of NSAIDs and PPI, Drug delivery systems.

1-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.

The anti-nociceptive action on NSAIDs is primarily due to the inhibition of prostaglandin biosynthesis through the inhibition of cyclooxygenase enzymes: COX-1(constitutive) and COX-2 (inducible in inflammatory processes).[6, 7]

Pantoprazole is 5-(Difluoromethoxy) - [[(3, 4- dimethoxy-2-Pyridiynyl) Methyl] sulphinyl]-1H -benzimidazole. It is gastric proton pump inhibitor.[8] The gastric proton pump inhibitors have structural resemblance to H2 antagonists. They are the prodrugs and after absorption get converted to reactive thiophilic sulphonamide cations. The sulphonamide reacts with the H+/K+AT-Pase, forming a covalent, disulphide linkage, thus irreversibly inactivating the enzyme.[9]

Fixed NSAID/PPI combinations will likely help to solve the gastrointestinal compliance problem. The first representative of this group of drugs for treating the signs and symptoms of osteo arithritis (OA), rheumatoid arithritis (RA), and ankylosing spondylitis, and for decreasing the risk of developing gastric ulcers in patients at risk has just been approved by the FDA.[10] An additional advantage of PPI combination is the lower incidence of heartburn, acid regurgitation, and sleep disturbance. Future guidelines will probably recommend combination of NSAIDs, as well as coxibs with a PPI, as first-line medication for all risk patients.[11]

The purpose of the present study was to make the co-medication of PPIs with NSAID in one formula to suppress gastric acid and obtain a combination of ketorolac in the form of solid dispersion as well as microencapsulation drug delivery systems using different types of polymers with pantoprazole in order to obtain a formula facilitating patient compliance and simplifying prescribing, improving efficacy with decreasing adverse effects aiming that their co-administration will result in decreasing the individual doses of each drug. Both drugs are simultaneously estimated using a unique analytical technique.

2- MATERIALS

Ketorolac tromethamine (Sigma- Aldrich, St. Louis, Mo, USA) was a gift sample kindly supplied by Amriya pharmaceuticals industries, Alexandria, Egypt , Pantoprazole (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.

3- METHODS

3.1. Preparation of solid dispersion

Three types of solid dispersion of ketorolac with Eudragit RS100, Eudragit RL100 and Ethyl cellulose (in a ratio 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.[12-14] The obtained product was kept in a desiccator over silica gel under reduced pressure until used. Pantoprazole was blended with the prepared solid dispersions in order to obtain a blend containing ketorolac solid dispersions with pantoprazole in a physical mixture form.

3.2. Coating of ketorolac with Eudragit RS100, Eudragit RL 100 and Ethyl cellulose

3.2.1. 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.[15,16]

3.2.2. 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 conditions in coating ketorolac powder.

Table (1): Operating Conditions in Coating Ketorolac Powder

Operating Conditions in Coating Ketorolac 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)

3.3. Granulation of pantoprazole: Wet granulation method was utilized for obtaining pantoprazole granules so as to prevent segregation of the drug if added to ketorolac solid dispersion or ketorolac microcapsules. Pantoprazole 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.

3.4. Determination of ketorolac and pantoprazole 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.[17-20]

3.5. 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 200–400 nm, delta wavelength 5nm and scaling factor 1.

3.5.1. Preparation of standard solutions and construction of calibration curves for ketorolac / pantoprazole formula

3.5.1.1. For ketorolac: 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 of 5-30 µg.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 (^{1}D) at 285.2 nm against the corresponding concentrations of the standard solutions. Stock standard solution of ketorolac was prepared similarly in phosphate buffer (pH 7.4) to obtain a final concentration of 1mg.ml^{-1}. Different aliquots from this stock solution were taken and diluted with the same buffer to obtain solutions of ketorolac in the concentration range of 5-30 µg.ml^{-1}. The zero order absorption spectra were recorded against phosphate buffer (pH 7.4) as a blank. Calibration curves were constructed by plotting the values of the first derivative absorbance (^{1}D) at 340 nm against the corresponding concentrations of the standard solutions.

3.5.1.2. For pantoprazole: Stock standard solution of pantoprazole 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 pantoprazole in the concentration

range of 5-30 µg.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 (^{1}D) at zero-crossing point for ketorolac 270.9 nm against the corresponding concentrations of the standard solutions.

Stock standard solution of pantoprazole was prepared similarly in phosphate buffer (pH 7.4) to obtain a final concentration of 1mg.ml$^{-1.}$ Different aliquots from this stock solution were taken and diluted with the same buffer to obtain solutions of pantoprazole in the concentration range of 5-30 µg.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 (^{1}D) at 227nm against corresponding concentrations of standard solutions**.**

3.6. *In vitro* drug release studies: The dissolution rate of ketorolac solid dispersions and its microcapsules equivalent to (10mg) as well as (20 mg) of pantoprazole 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 1.0 (0.1 N HCL) and pH 7.4 (phosphate buffer). Paddle speed of 100 rpm and temperature of 37.5^{o}C±0.2 were employed. Aliquots (5ml) were withdrawn, filtered through 0.45µm membrane filter and replaced with equal volumes of prewarmed fresh medium to maintain constant volume and keep sink condition.

The drug' 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.

3.3. Assay of the prepared blend

3.3.1. Simultaneous determination of ketorolac and pantoprazole

The zero order spectrum of this aliquot of dissolution medium was recorded against 0.1 N HCl (dissolution medium 1) or phosphate buffer (pH 7.4) (dissolution medium 2) as blank.

For dissolution medium (1): the ^1D value was recorded at 285.2 and at 270.9 for determination of ketorolac and pantoprazole 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 340 and at 227 for determination of ketorolac and pantoprazole respectively, then the concentration of each drug was calculated from the corresponding regression equation of its calibration curve.

3- RESULTS AND DISCUSSION

a- For the first formula (ketorolac and pantoprazole)

Since the zero-order spectra of ketorolac and pantoprazole in 0.1 N HCL (pH 1.0) and in phosphate buffer (pH 7.4) are overlapping as shown in Fig.1(A) and Fig.2 (A) respectively, the determination of both ingredients utilizing the conventional UV spectrophotometry has become invalid. A first derivative spectrophotometric method was adopted for their simultaneous determination where the first derivative spectra revealed zero-crossing point for pantoprazole allowing the measurement of ketorolac and the contrary zero-crosses points for ketorolac allowing the measurement of pantoprazole Fig. 1(B) and Fig. 2 (B).

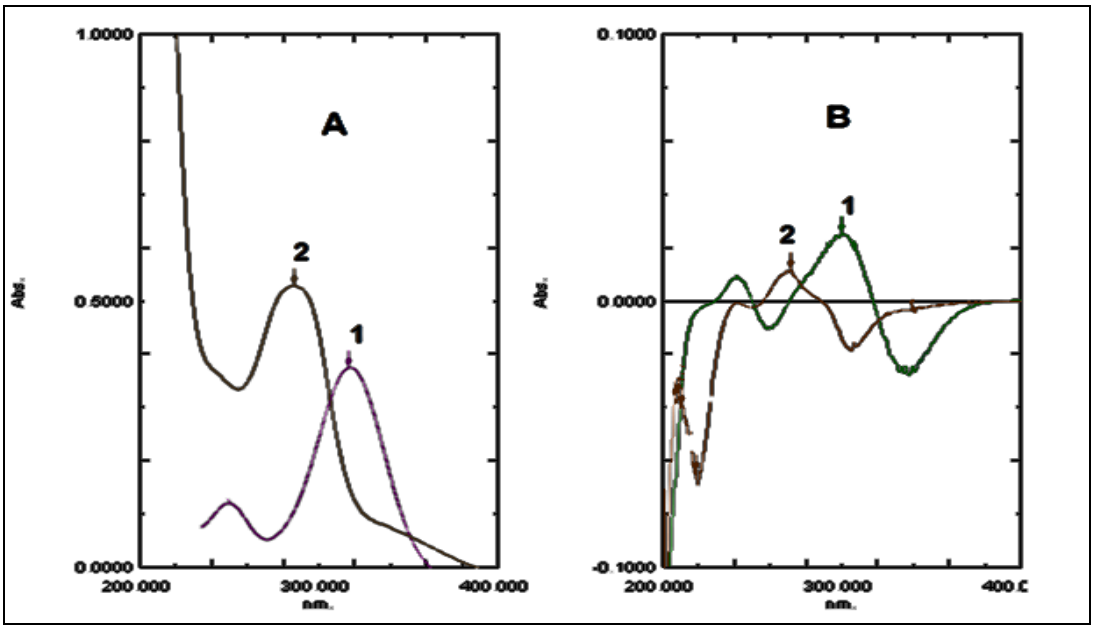

Fig (1) Overlain of zero-order spectra (A) for ketorolac (1) & pantoprazole (2) and 1st order spectra (B) for ketorolac (1) & pantoprazole (2) in phosphate buffer (pH 1.0)

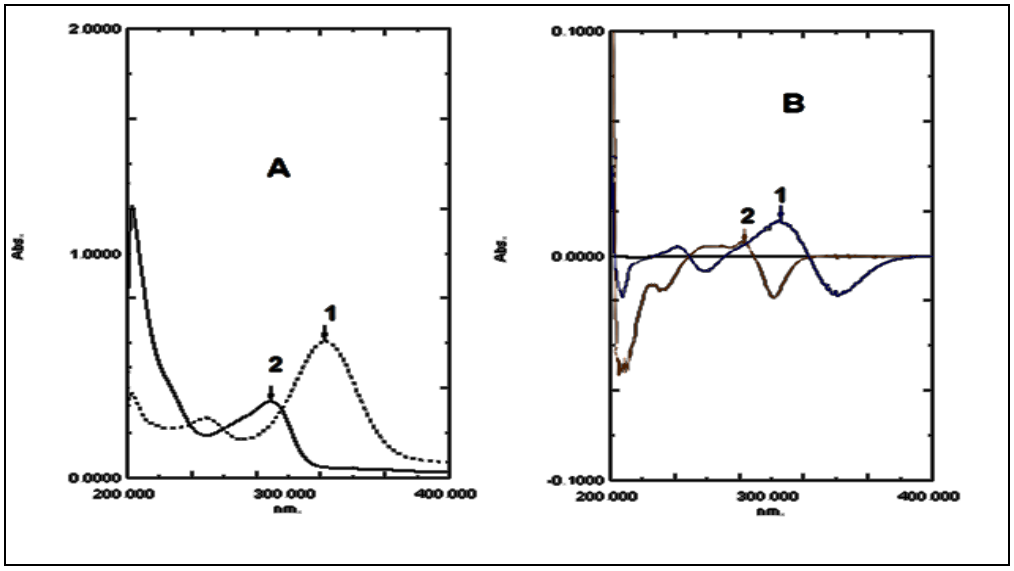

Fig (2) Overlain of zero-order spectra (A) for ketorolac (1) & pantoprazole (2) and 1st order spectra (B) for ketorolac(1) & pantoprazole (2) in phosphate buffer (pH 7.4)

4.1. Validation of the proposed first derivative spectrophotometric method for first formula: The Validity of the method was tested regarding linearity, specificity, accuracy, and precision according to ICH guide lines (ICH-Q2B, 2005).[21]

4.1.1. Linearity and range: The calibration graphs for the determination of ketorolac and pantoprazole 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).

Table 2: Statistical data of calibration curves of ketorolac and pantoprazole

Parameter	In pH 1.0		In pH 7.4	
	ketorolac	pantoprazole	ketorolac	pantoprazole
Linearity Range ($\mu g.ml^{-1}$)	5- 30	5- 30	5- 30	5-30
Regression equation	$^1D_{285.2}$=0.0013x-0.0004	$^1D_{270.9}$=0.0007x+0.006	$^1D_{340}$= 0.0015x-0.0012	$^1D_{227}$=0.0022x+0.0002
Correlation coefficient	0.999	0.999	0.9999	1
SD about slope	0.000002	0.00017	0.0016	0.0004
SD about intercept	0.00040	0.001300	0.0003	0.00200
LOD ($\mu g.ml^{-1}$)	0.41000	0.34000	0.4000	0.3000
LOQ ($\mu g.ml^{-1}$)	1.2300	1.0600	1.1300	0.900

Statistical analysis of the data showed 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.

4.1.2. 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 (2). LOQ and LOD were calculated according to the following equations[21]

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.

4.1.3. Accuracy and precision: To prove the accuracy of the proposed methods several synthetic mixtures of ketorolac and pantoprazole in the ratio 1:1 were analyzed.

Statistical analysis of the obtained results involving the mean percent recoveries of both drugs in the proposed mixtures are summarized in Tables 3 and 4.

Table (3) Recovery of synthetic mixtures of ketorolac and pantoprazole

drug	Concentration (µg.ml^{-1})	Mean* % recovery	
		In pH 1.0	In pH 7.4
ketorolac	10	99.30±0.06	102.00±0.08
	20	99.00±0.19	99.57±0.02
	30	100.30±0.03	99.80±0.14
pantoprazole	10	100.10±0.09	99.70±0.02
	20	99.95±0.07	100.22±0.06
	30	99.73±0.01	99.68±0.04

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

Table (4): Precision data for the determination of ketorolac and pantoprazole

drug	Concentration ($\mu g.ml^{-1}$)	Intra-day *		Inter-day *	
		Concentration found ($\mu g.ml^{-1}$)		Concentration found ($\mu g.ml^{-1}$)	
		In pH 1.0	In pH 7.4	In pH 1.0	In pH 7.4
ketorolac	10	9.98±0.02	9.97±0.04	9.98±0.06	9.98±0.01
	20	20.01±0.12	20.05±0.02	19.99±0.12	19.97±0.05
	30	29.98±0.03	29.99±0.01	30.01±0.14	30.03±0.03
pantoprazole	10	9.99±0.04	10.20±0.02	9.99±0.02	9.99±0.07
	20	19.97±0.01	19.99±0.12	19.98±0.09	19.96±0.01
	30	30.03±0.05	29.99±0.06	29.99±0.01	29.98±0.08

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

Intraday (repeatability) and inter-day (intermediate) precisions were assessed using three concentrations. 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.

3.2. *In- vitro* drug release from solid dispersion systems: The release profile of ketorolac solid dispersions prepared from different types of polymers (Eudragit RS100, Eudragit RL100 and Ethyl cellulose) as well as the dissolution of pantoprazole present as a physical mixture are presented in Table 5 and 6 (pH 1.0 and pH 7.4) respectively.

Table (5): Simultaneous dissolution of ketorolac solid dispersion in combination of pantoprazole physical mixture at pH 1.0

Time (min) / Drug		% Drug Released *		
		Polymer used in Solid Dispersion		
		Eudragit RS 100	Eudragit RL 100	Ethyl Cellulose
5	a	0.00	0.25±0.57	0.44±0.78
	b	6.15±0.13	6.26±0.22	6.88±0.40
10	a	0.00	0.56±0.90	0.65±0.55
	b	7.86±0.24	7.32±0.78	7.75±0.32
15	a	0.46±0.69	0.97±0.65	1.17±0.86
	b	9.14±0.22	9.80±0.30	10.04±0.74
20	a	0.66±0.35	1.49±0.58	1.70±0.35
	b	10.89±0.70	10.93±0.81	11.21±0.47
30	a	0.90±0.21	1.91±0.61	2.08±0.94
	b	12.33±0.73	12.76±0.56	12.96±0.32
45	a	1.48±0.37	2.45±0.58	2.41±0.30

	b	15.19±03	14.95±0.20	15.44±0.64
60	**a** **b**	1.93±0.25 18.29±0.45	2.74±0.19 17.85±0.32	2.92±0.79 18.73±0.07
90	**a** **b**	2.29±0.60 21.49±0.11	3.08±0.73 21.02±0.19	3.17±0.36 22.07±0.66
120	**a** **b**	3.09±0.05 24.51±0.80	3.45±0.29 23.79±0.83	3.62±0.04 25.11±0.32

a: ketorolac b: pantoprazole

It is clear from Table (5) that the percentage of ketorolac released from the solid dispersions over the experimental time period (120min) were 3.09±0.05, 3.45±0.29 and 3.62±0.04 from Eudragit RS100, Eudragit RL100 and Ethyl cellulose respectively. The percentage of pantoprazole dissolved from the physical mixture contained with solid dispersions were 24.51±0.807, 23.79±0.83and 25.11±0.32 respectively.

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

Time (hrs) / **Drug**		**% Drug Released ***		
		Polymer used in Solid Dispersion		
		Eudragit RS 100	**Eudragit RL 100**	**Ethyl Cellulose**
0.50	**a** **b**	18.12±0.45 27.16±0.30	20.22±0.98 28.12±0.04	23.71±0.64 29.21±0.46
0.75	**a** **b**	21.33±0.39 31.89±0.11	22.99±0.50 32.65±0.70	27.44±0.64 33.03±0.08
1.00	**a** **b**	23.78±0.21 38.01±0.33	25.95±0.11 38.67±0.90	30.70±0.01 39.43±0.32
1.50	**a** **b**	27.49±0.70 40.98±0.24	30.01±0.54 41.16±0.74	35.08±0.34 42.22±0.46
2.00	**a** **b**	31.70±0.04 45.96±0.08	33.19±0.29 46.37±0.36	38.14±0.67 47.24±0.57
4.00	**a** **b**	34.54±0.20 52.87±0.53	37.30±0.10 53.25±0.12	45.89±0.32 54.07±0.41
6.00	**a** **b**	39.07±0.73 66.79±0.37	41.98±0.70 67.12±0.83	49.45±0.08 67.91±0.28
8.00	**a** **b**	42.90±0.14 72.56±0.33	45.32±0.88 73.35±0.08	58.63±0.53 74.10±0.02
10.00	**a** **b**	47.12±0.52 80.09±0.36	50.16±0.60 80.90±0.77	63.36±0.22 81.28±0.42
12.00	**a** **b**	49.53±0.90 91.73±0.23	53.11±0.59 92.29±0.31	67.29±0.52 93.03±0.22

a: ketorolac b: pantoprazole

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 18.12±0.45, 21.45±0.43and 23.71±0.64 from Eudragit RS100, Eudragit RL100 and Ethyl cellulose respectively after 0.5hour. After 12 hours the percentages were 49.53±0.90, 53.11±0.42and 67.29±0.52respectively, this means that a controlled drug release all over the experimental time is obtained. From Table 5 and 6, it is clear that over 50% of ketorolac e 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.

3.3. *In- vitro* drug release from microcapsules: The release profile of ketorolac microcapsules systems prepared from different types of polymers (Eudragit RS100, Eudragit RL100 and Ethyl cellulose) as well as the dissolution of pantoprazole present as a physical mixture are presented in Table 7 and 8 (pH 1.0 and pH 7.4) respectively.

Table (7): Simultaneous dissolution of ketorolac microcapsules in combination of pantoprazole physical mixture at pH 1.0

Time (min) / Drug		% Drug Released *		
		Polymer used in Solid Dispersion		
		Eudragit RS 100	Eudragit RL 100	Ethyl Cellulose
5	a	0.00	0.00	0.00
	b	6.81±0.33	6.14±0.57	6.03±0.36
10	a	0.00	0.00	0.00
	b	7.22±0.56	7.45±0.69	7.08±0.75
15	a	0.28±0.11	0.35±0.29	0.52±0.33
	b	9.14±0.22	9.80±0.30	10.04±0.74
20	a	0.50±0.75	0.60±0.83	0.82±0.35
	b	11.04±0.24	10.58±0.70	10.78±0.16
30	a	0.83±0.64	1.03±0.22	1.12±0.38
	b	12.54±0.56	12.18±0.80	12.86±0.07
45	a	0.95±0.07	1.54±0.78	1.69±0.30
	b	15.82±74	15.05±0.12	14.97±0.41
60	a	1.34±0.17	1.90±0.09	2.01±0.79
	b	18.13±0.74	18.44±0.40	17.84±0.29
90	a	1.81±0.54	2.28±0.20	2.43±0.08
	b	22.32±0.48	21.70±0.32	21.88±0.18
120	a	1.99±0.90	2.69±0.18	2.87±0.88
	b	25.06±0.17	24.55±0.37	24.63±0.46

a: ketorolac b- pantoprazole

It is clear from Table (7) that the percentage of ketorolac released from the microcapsules over the experimental time period (120 min) were 1.99±0.90, 2.69±0.18 and 2.87±0.88 from Eudragit RS100, Eudragit RL100 and ethyl cellulose respectively. The percentage of pantoprazole dissolved from the physical mixture contained with microcapsules were 25.06±0.17, 24.55±0.37and 24.63±0.46 respectively.

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

Time (hrs) / Drug		% Drug Released *		
		Polymer used in Solid Dispersion		
		Eudragit RS 100	Eudragit RL 100	Ethyl Cellulose
0.50	a	16.66±0.21	17.00±0.63	18.70±0.21
	b	29.13±0.94	28.93±0.73	29.02±0.27
0.75	a	19.29 ±0.38	20.86±0.23	21.86±0.35
	b	33.08±0.39	31.98±0.17	32.55±0.38
1.00	a	20.89±0.90	21.04±0.27	25.87±0.34
	b	39.01±0.15	38.79±0.42	38.88±0.04
1.50	a	23.96±0.16	24.67±0.22	29.55±0.07
	b	42.32±0.24	41.78±0.53	42.06±0.23
2.00	a	26.94±0.81	27.26±0.08	33.61±0.58
	b	47.03±0.25	46.45±0.22	45.99±0.62
4.00	a	29.75±0.53	30.99±0.21	38.11±0.40
	b	54.36±0.22	53.42±0.40	52.95±0.74
6.00	a	32.73±0.20	39.90±0.11	44.45±0.08
	b	67.19±0.73	66.76±0.32	67.93±0.11
8.00	a	37.09±0.92	40.21±0.43	50.00±0.81
	b	74.02±0.43	73.85±0.44	73.54±0.61
10.00	a	40.99±0.38	47.32 ±0.11	52.99±0.42
	b	81.32±0.36	80.96±0.52	81.01±0.47
12.00	a	45.02±0.30	50.40±0.21	55.32±0.80
	b	93.07±0.95	92.75±0.08	92.83±0.03

a: ketorolac b- pantoprazole

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 16.66±0.21, 17.00±0.63 and 18.70±0.21 from Eudragit RS100, Eudragit RL100 and ethyl cellulose respectively after 30min. After 12 hours the percentages were 45.02±0.30, 50.40±0.21 and 55.32±0.80 respectively, this means that a controlled drug release all over the experimental time is obtained. From table 7and 8, it is clear that over 45% of ketorolac are available to be released and absorbed from the intestine under the effect of the polymers chosen for the microcapsules.

These results show that the microencapsulation technique played a great role in reducing the gastro-toxic side effects of the drug such as peptic ulcer.

In a previous study in our laboratory the authors proved that there is no interaction between ketorolac and the polymers used in this study.[22]

CONCLUSION

The previous results show that microencapsulation technique has a great role in coating efficiency a well as in drug release compared with solid dispersion technique. Microencapsulation technique played a great role in reducing the gastro-toxic side effects of ketorolac. Co-administration of combination of NSAID and PPIs is the best agents for the therapy and prophylaxis of NSAIDs and ASA-associated GI injury.

REFERENCES

1. M. S. Catapano, The analgesic efficacy of ketorolac for acute pain. J. Emerg. Med. 1996, 14: 67-75.
2. J. A. Mitchell, T. D. Warner, Cyclooxygenase 2, pharmacology, physiology, biochemistry and relevance to NSAIDs therapy. Br. J. Pharmacol, 1999; 128: 1121-1132.
3. A. L. Smith, D. L. Dewitt, R. M. Garavito, Cyclooxygenases: structural, cellular, and molecular biology. Ann. Rev. Biochem. 2000; 69: 145-182.
4. B. Estenne, M. Julien, H. Charleux, Comparison of ketorolac, pentazocine and placebo in treating postoperative pain. Curr. Ther. Ros. 1988; 43: 1182-1183.
5. J. P. Yee, J. E. Koshiver, C. Allbon, C. R. Brown, Comparison of intra- muscular ketorolac tromethamine and morphine sulfate for analgesia of pain after major surgery. Clin. Pharmacol. Ther. 1986; 273: 253-261.
6. A. K. Maiti, A. K. Dhara, A Nanda Preparation and evaluation of starch coated alginate microsphere of diclofenac potassium Int. J. Pharm. Tech. Res. 2012, 4: 630-636.
7. Physicians' Desk reference, Medical Economics Company Inc., 56th ed., Mantvale, NJ, 2002 pp 2685.
8. Merck Index-an encyclopedia of chemicals, drugs and biologicals, 13th edition 2011; 7084.
9. Y. Loke, A. Trivedi, S. Singh, Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs, Aliment. Pharm. Ther. 2008; 27(1): 31-40.

10. F. Chan, L. Hung, B. Suen, Celecoxib versus diclofenac and omeprazole in reducing the risk of recurrent ulcer bleeding in patients with arthritis, J. Med. Engl. 2002; 10: 347-2104.
11. F. Chan, V. Wong, B. Suen, Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomized trial, Aliment. Pharm. Ther. 2007; 6: 369-1621.
12. A. Sera juddin, solid dispersion technique. J. Pharm. Sci. 1999; 88(10): 891-900.
13. G. Rassu, E. Gavini, G. Spanda, P. Giunchedi, S. Morceddu, Ketoprofen spray-dried microspheres based on Eudragit RS and RL; study of the manufacturing parameters. Drug Dev. Ind. Pharm. 2008; 34(11): 1178-1187.
14. T. Sudhamani, K.N. Reddy, V.R. Kumar, R. Revathi, V. Ganesan, Preparation and evaluation of ethyl cellulose microspheres of Ibuprofen for sustained drug delivery. Int. J. Pharm. Res. Dev. 2010; 2(8): 119-125.
15. S.M. Wong, I.W. Kellaway, S. Murdan, Enhancement of the dissolution rate and oral absorption of a poorly water soluble drug by formation of surfactant-containing microparticles. Int. J. Pharmaceutics, 2006; 317(1): 61-68.
16. M. Meshali, E. Zein El- Dien, S.A. Omar, L.A. Luzzi, A new approach to encapsulating non-steroidal anti-inflammatory drugs; Bioavailability and gastric ulcerogenic activity I. J. of Microencapsulation, 1987a; 4: 133-190.
17. F. Sánchez, C. Bosch, J. Cano, Recent development in derivative ultraviolet/visible absorption spectrophotometry. Talanta. 1988; 35: 753.
18. C. Bosch, F. Sanchez, Recent development in derivative ultraviolet/visible absorption spectrophotometry. Talanta, 1995; 42: 1195.
19. M. Mabrouk, H. El-Fatatry, Sherin Hammad, M. Abdel Aziz, Simultaneous determination of loratadine and pseudoephedrine sulfate in pharmaceutical formulation by RPLC and derivative spectrophotometry. J. Pharm. Biomed. Anal. 2003; 33: 597.
20. C. Bosch, J. Cano, Recent development in derivative ultraviolet/visible absorption spectrophotometry. Analytica Chimica Acta. 2009; 635: 22.
21. ICH Harmonized Tripartite Guideline, Validation of Analytical Procedures. Text and Methodology, Q2 (R1), Current Step 4 Version. Parent Guidelines on Methodology, (2005).
22. S.A. El-Gizawy, E.E. Zein El Din, A.A. Donia H. A. Yassin Formulation, in-vitro and in-vivo evaluation of ketorolac tromethamine controlled release drug delivery system World J. Pharm. Sci. 2014; 2(8): 793-806.