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SOLID DISPERSION AND IONOTROPIC GELATION TECHNIQUE FOR OBTAINING CONTROLLED DRUG DELIVERY SYSTEM CONTAINING DICLOFENAC AND PANTOPRAZOLE

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ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAID) are among the most commonly prescribed agents for rheumatic disorders such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis. 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 diclofenac/pantoprazole formula was been studied. An accurate simple and précised method was adopted for simultaneous determination of diclofenac and pantoprazole in a physical mixture form. The method is based on measuring the first derivative amplitudes at 285.20 nm and 272.60 nm for diclofenac and pantoprazole respectively in 0.1N HCl using 0.1N HCl as a blank. The first derivative values of absorbance at 288.90 nm and 275.60 nm were measured for diclofenac and pantoprazole respectively in phosphate buffer (pH7.4) using phosphate buffer (pH7.4) as a blank. The obtained results were validated for accuracy, precision, LOD, LOQ and were found to be satisfactory. The proposed method is sample, rapid and suitable for the assay of such combinations.

KEYWORDS: osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

1-INTRODUCTION

Diclofenac sodium or sodium-2-[(2, 6-dichlorophenyl) amino] phenyl] acetate, is widely used as NSAID in therapeutics, it inhibits the cyclooxygenase enzyme1. Diclofenac sodium is used

as analgesic, antipyretic, anti-inflammatory and approved in the United States for the long term symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.[1]

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).[2, 3]

Pantoprazole is 6-(difluoromethoxy)-2- [(3, 4-dimethoxypyridin-2-yl methane] sulfinyl-1H-1, 3- benzodiazole. Pantoprazole is a proton pump inhibitor drug used for short-term treatment of erosion and ulceration of the esophagus caused by gastro esophageal reflux disease.[4] Pantoprazole is a PPI that suppresses the final step in gastric acid production by forming a covalent bond to two sites of the (H+,K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell.[5]

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 OA, RA, and ankylosing spondylitis, and for decreasing the risk of developing gastric ulcers in patients at risk has just been approved by the FDA.[6] 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.[7]

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 diclofenac in the form of solid dispersion as well as microbeads 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

Diclofenac sodium (Sigma- Aldrich, St. Louis, Mo, USA) was a gift sample kindly supplied by Pharco Pharmaceuticals industries, Ismailia, Egypt, Pantoprazole (Sigma-Aldrich, St. Louis, Mo, USA) was a gift sample kindly supplied by Sigma pharmaceuticals industries,

Quweisna, Egypt. Eudragit RS100 and Eudragit RL100 were purchased from RÖhm Pharma GMBH, Darmstadt (Germany), Ethyl cellulose; HPMC and sodium alginate were obtained from Sigma-Aldrich Chemi (Germany). All other reagents and chemicals were analytical grades and were used as received.

3- METHOD

3.1. Preparation of solid dispersion

Three types of solid dispersion of diclofenac 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 40o 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.[8-10] The obtained product was kept in a desiccator over silica gel under reduced pressure until used.

3.2. Preparation of microbeads

Microbeads of diclofenac sodium were prepared by ionotropic gelation technique. In this present work four sets of microbeads were prepared by using sodium alginate alone and combination with coating polymers like HPMC and calcium chloride used as counter ion.

The microbeads were prepared in an environment free from organic solvents by dropping a mixture of colloidal copolymer dispersion, the dispersed drug diclofenac sodium, formed mucilage of sodium alginate in calcium chloride solution, which acted as a counter ion. The droplets instantaneously formed gelled spherical beads due to cross-linking of calcium ion with the sodium ion which remain ionized in the solution.[11]

Chemical reaction between sodium alginate and calcium chloride to form calcium alginate was utilized for the microencapsulation of diclofenac sodium core material. Preliminary work on the preparation of microbeads revealed that stirring speed and curing time greatly affected the size of microbeads.[12] Smaller particles can be prepared by adjusting stirring rate to 500rpm and curing time for 2h and also depending upon the height of the syringe from the

level of counter ion solution, compressed force on the plunger of the syringe. The gelled particles were cured to get sufficiently hardened beads, filtered, washed and dried. The colloidal polymer particles fused into the polymer matrix during drying with the drug being dispersed in the latex.

3.2.1. Preparation of Alginate-HPMC microbeads

Microbeads were prepared using sodium alginate and HPMC as coating polymers. To 50ml of deionized water, HPMC was added and stirred with an electric stirrer to form mucilage. Sodium alginate was added to form uniform dispersion. Weighed quantity of diclofenac sodium was added and homogenized for 5 min. The resulting dispersion was dropped through a syringe with a needle into 100ml of 5%w/v aqueous calcium chloride solution and stirred at 500rpm. After stirring for 30min the formed beads were separated by filtration, washed with distilled water, dried at 70oC for 6h in an oven.[13]

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 diclofenac solid dispersion or diclofenac microbeads. 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. Determinations of diclofenac 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.[14-17]

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 diclofenac/ pantoprazole formula

3.5.1.1. For diclofenac

Stock standard solution of diclofenac 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 diclofenac 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 (1D) at 285.20 nm against the corresponding concentrations of the standard solutions.

Stock standard solution of diclofenac 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 diclofenac 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 (1D) at 288.90 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 (1D) at zero-crossing point for ketorolac 272.60 nm against the corresponding concentrations of standard solutions.

Stock standard solution of pantoprazole was prepared similarly 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 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 (1D) at 275.60 nm against corresponding concentrations of standard solutions.

3.6. *In vitro* drug release studies

The dissolution rate of diclofenac solid dispersions and its microbeads equivalent to (50mg) 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 37.5oC±0.2 were employed. Aliquots (5ml) were withdrawn, filtered through 0.45 membrane filter 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 spectrophotometrically with respect to time. Studies were performed in triplicate for each sample and the results were reported as mean ± SD.

3.7. Assay of the prepared blend

3.7.1. Simultaneous determination of diclofenac 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 285.20 nm and at 272.60 nm for determination of diclofenac 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 288.90 nm and at 275.60 nm for determination of diclofenac and pantoprazole respectively, then the concentration of each drug was calculated from the corresponding regression equation of its calibration curve.

3- RESULTS AND DISCUSSION

Since the zero-order spectra of diclofenac 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 diclofenac and the contrary zero-crosses points for diclofenac allowing the measurement of pantoprazole Fig. 1 (B) and Fig. 2 (B).

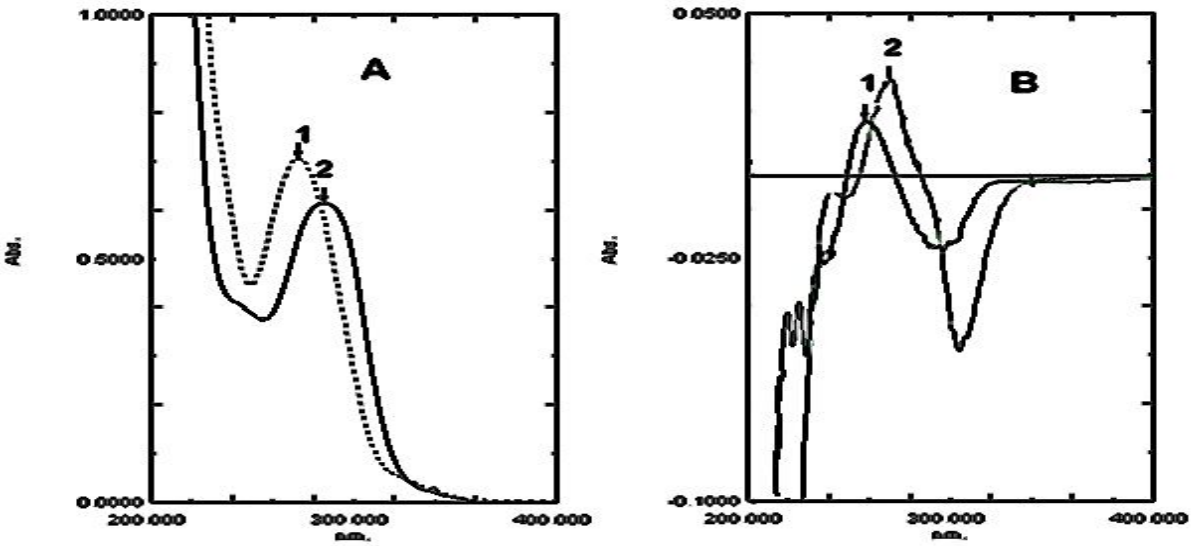

Fig (1) Overlain of zero-order spectra (A) for diclofenac (1) & pantoprazole (2) and 1st order spectra (B) for diclofenac (1) & pantoprazole (2) in phosphate buffer (pH 1.0)

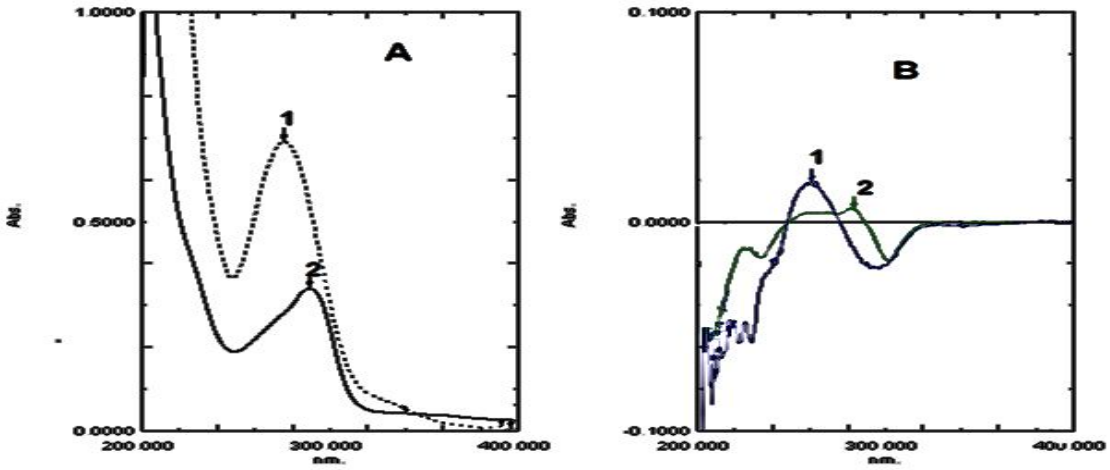

Fig (2) Overlain of zero-order spectra (A) for diclofenac (1) & pantoprazole (2) and 1st order spectra (B) for diclofenac (1) & pantoprazole (2) in phosphate buffer (pH 7.4)

3.1. 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).[18]

3.1.1. 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 (1).

Table 1: Statistical data of calibration curves of diclofenac and pantoprazole

Parameter	In pH 1.0		In pH 7.4	
	diclofenac	pantoprazole	diclofenac	pantoprazole
Linearity Range (µg.ml^{-1})	5- 30	5- 30	5- 30	5-30
Regression equation	$^{1}D_{285.2}$= 0.0007x-0.0001	$^{1}D_{272.6}$= 0.0008x-0.002	$^{1}D_{288.9}$=0.0007x-0.003	$^{1}D_{275.6}$=0.005x+0.001
Correlation coefficient	0.999	0.999	0.9999	0.9999
SD about slope	0.000001	0.00013	0.0012	0.0002
SD about intercept	0.00001	0.00003	0.0002	0.00400
LOD (µg.ml^{-1})	0.43000	0. 41000	0.4000	0.33000
LOQ (µg.ml^{-1})	1.400	1.2300	1.3200	1.100

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.

3.1.2. Limit of Detection (LOD) and Limit of Quantitation (LOQ) for the formula

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 [18]:

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.

3.1.3. Accuracy and precision for formula

To prove the accuracy of the proposed methods several synthetic mixtures of diclofenac and pantoprazole in the ratio 1:1 were analyzed.

Statistical analysis of the obtained results involving the mean percent recoveries of both drugs in these mixtures are summarized in Tables 2 and 3.

Table (2) Recovery of synthetic mixtures of diclofenac and pantoprazole

drug	Concentration ($\mu g.ml^{-1}$)	Mean* % recovery	
		In pH 1.0	In pH 7.4
diclofenac	10	99.30±0.06	102.00±0.02
	20	99.00±0.19	99.57±0.08
	30	100.30±0.03	99.80±0.14
pantoprazole	10	100.10±0.09	99.70±0.11
	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 (3): Precision data for the determination of diclofenac 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
diclofenac	10	9.97±0.01	9.99±0.16	9.98±0.02	10.00±0.03
	20	20.04±0.02	20.06±0.05	19.99±0.14	19.98±0.01
	30	29.99±0.22	29.98±0.02	30.04±0.04	29.99±0.02
pantoprazole	10	10.00±0.03	10.10±0.09	9.99±0.01	9.98±0.06
	20	19.98±0.05	20.21±0.11	19.99±0.07	19.97±0.04
	30	30.01±0.13	29.97±0.08	29.99±0.05	30.05±0.13

***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 3.

3.2. *In- vitro* drug release from solid dispersion systems

The release profile of diclofenac 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 4 and 5 (pH 1.0 and pH 7.4) respectively.

Table (4): Simultaneous dissolution of diclofenac 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	0.00	0.26±0.31
	b	6.22±0.63	6.87±0.19	7.02±0.26
10	a	0.0	0.48±0.90	0.58±0.32
	b	7.92±0.73	7.47±0.80	8.11±0.38
15	a	0.40±0.54	0.60±0.22	0.68±0.43
	b	9.34±0.27	9.78±0.18	10.20±0.40
20	a	0.61±0.32	0.94±0.34	0.98±0.19
	b	10.56±0.83	10.33±0.06	11.45±0.10
30	a	0.89±0.11	1.22±0.07	1.28±0.76
	b	12.71±0.73	12.12±0.36	13.04±0.09
45	a	1.41±0.28	1.94±0.45	2.08±0.06
	b	15.16±0.50	14.89±0.14	15.70±0.21
60	a	1.88±0.40	2.32±0.76	2.56±0.39
	b	18.07±0.33	17.75±0.45	18.78±0.68
90	a	2.15±0.80	2.61±0. 76	2.81±0.50
	b	21.79±0.29	21.06±0.77	22.31±0.76
120	a	2.76±0.78	2.86±0.87	3.42±0.31
	b	24.33±0.47	23.86±0.44	25.53±0.41

a: diclofenac b: pantoprazole

The results are the mean of 3 readings ± SD.

It is clear from table (4) that the percentage of diclofenac released from the solid dispersions over the experimental time period (120 min) were 2.76±0.78, 2.86±0.87 and 3.42±0.31 from Eudragit RS100, Eudragit RL100 and ethyl cellulose respectively. The percentage of pantoprazole dissolved from the physical mixture contained with solid dispersions were 24.33±0.47, 23.86±0.44and 25.53±0.41 respectively.

Table (5): Simultaneous dissolution of diclofenac 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	20.03±0.11	21.45±0.43	23.98±0.64
	b	28.17±0.34	29.12±0.64	27.88±0.35
0.75	a	23.24±0.78	25.08±0.31	26.85±0.39
	b	32.79±0.85	33.21±0.67	32.13±0.08
1.00	a	26.05±0.50	27.88±0.58	29.66±0.21
	b	38.81±0.32	39.81±0.22	38.02±0.41
1.50	a	30.98±0.09	32.55±0.34	34.67±0.34
	b	41.64±0.08	42.07±0.64	41.16±0.39
2.00	a	35.22±0.86	36.98±0.17	40.35±0.67
	b	46.88±0.19	47.45±0.51	46.12±0.77
4.00	a	42.07±0.82	43.86±0.22	46.21±0.32
	b	53.19±0.81	54.25±0.90	52.98±0.18
6.00	a	46.33±0.64	47.98±0.69	53.89±0.08
	b	67.08±0.10	67.99±0.07	66.45±0.21
8.00	a	53.78±0.45	54.97±0. 31	61.56±0.53
	b	73.59±0.41	74.22±0.45	72.12±0.54
10.00	a	57.12±0.34	58.75±0.39	68.25±0.22
	b	80.35±0.72	81.56±0.93	80.02±0.71
12.00	a	60.58±0.21	62.05±0.42	74.79±0.52
	b	92.16±0.79	93.29±0.61	91.87±0.31

a: diclofenac b: pantoprazole

From table (5), it is obvious that at pH 7.4 a controlled process of diclofenac percentage release from the solid dispersions and the subsequent dissolution began by 20.03±0.11, 21.45and 23.98±0.64from Eudragit RS100, Eudragit RL100 and ethyl cellulose respectively after 0.5hour. After 12 hours the percentages were 60.58±0.21, 62.05±0.42and 74.79±0.52 respectively, this means that a controlled drug release all over the experimental time is obtained.

From table 4 and 5, it is clear that over 60% of diclofenac 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 microbeads

The release profile of diclofenac microbeads prepared from different types of polymers (HPMC, and sodium alginate) as well as the dissolution of pantoprazole present as a physical mixture are presented in Table 6 (pH 1.0 and pH 7.4) respectively.

Table (6): Simultaneous dissolution of diclofenac microbeads in combination of pantoprazole physical mixture

Time		Drug	% Drug Released	
Min*	Hrs.**		pH 1.0*	pH 7.4**
5	0.50	a b	0.00 6.00±0.24	7.65±0.18 29.05±0.33
10	1.00	a b	0.0 7.46±0.37	15.25±0.44 39.11±0.80
15	1. 50	a b	0.00 8.99±0.69	19.13±0.63 42.51±0.22
20	2.00	a b	0.48±0.64 10.21±0.49	22.98±0.23 45.78±0.77
30	4.00	a b	0.88±0.31 11.79±0.56	29.08±0.36 54.02±0.38
45	6.00	a b	1.25±0.39 14.78±0.67	35.22±0.03 76.90±0.46
60	8.00	a b	1.46±0.5 17.43±0.23	40.53±0.39 74.54±0.35
90	10.00	a b	1.82±0.43 21.11±0.67	43.11±0.67 81.36±0.53
120	12.00	a b	2.26±0.25 24.65±0.34	45.28±0.06 93.29±0.72

a: diclofenac b: pantoprazole

It is clear from table (6) that the percentage of diclofenac released from the microbeads over the experimental time period (120 min) at pH 1.0 was 2.26±0.25 from HPMC-sodium alginate microbeads. The percentage of pantoprazole dissolved from the physical mixture contained with microbeads was 24.65±0.34. It is clear that over 45% of diclofenac is available to be released and absorbed from the intestine under the effect of the polymers chosen for the microbeads after 12 hours.

It is clear from table (6) that the percentage of diclofenac released from the microbeads over the experimental time period (120 min) at pH 1.0 was 2.26±0.25 from HPMC-sodium alginate microbeads. The percentage of pantoprazole dissolved from the physical mixture contained with microbeads was 24.65±0.34. It is clear that over 45% of diclofenac is

available to be released and absorbed from the intestine under the effect of the polymers chosen for the microbeads after 12 hours.

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 diclofenac and the polymers used in this study.[19, 20]

4- 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 diclofenac. Co-administration of combination of NSAID and PPIs is the preferred agents for the therapy and prophylaxis of NSAIDs and ASA-associated GI injury.

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