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IN-VITRO EVALUATION AND KINETIC ESTIMATION OF A PROPOSED DRUG DELIVERY SYSTEM CONTAINING KETOROLAC

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ABSTRACT

In the present study, solid dispersion technique was used in order to control the release of ketorolac using EudragitRS100, EudragitRL100 and ethyl cellulose in ratios of 1:1, 1:2 and 1:3 (drug to polymer) to overcome the drug related adverse effects, improve drug bioavailability in different GI tract conditions. All investigated properties showed satisfactory results. By increasing concentration of the polymers in the formula; there was increase in size distribution as well as flow properties. Drug-polymer interactions were not observed in FT-IR studies. The drug content in all of the proposed formulations was in the range of 96.45 to 102.20%. The physical state of the drug in the formulation was determined by Differential Thermal Analysis (DTA). In-vitro drug release profile of ketorolac from the proposed formulations was examined in simulated gastric fluid (SGF pH1.0) and simulated intestinal fluid (SIF pH7.4). All prepared formulations showed optimum level of controlled release and exhibited Higuchi kinetics.

KEYWORDS: Ketorolac, Controlled release system, Solid dispersion, Oral drug delivery system.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing processes. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with acceptable levels of safety to the patient (Brahma et al., 2002).

In the recent years a wide variety of newer oral drug delivery systems like controlled release dosage forms are designed and evaluated in order to overcome the limitations of conventional therapy. These products are able to maintain steady drug plasma levels for extended periods of time as a result the variations of the drug levels in the blood are prevented and minimized drug related side effects (Maderuelo et al., 2011).

The non-steroidal anti-inflammatory drug ketorolac is a good candidate for the development of oral controlled release formulations. It is used for the treatment of rheumatoid arthritis, osteoarthritis with dose range 10-20mg 2-3 times, as conventional tablets/capsules (Maheshwari, 2007).

An adverse gastrointestinal reaction has been observed and due to its short biological half-life requires multiple dosing. It leads to fluctuation in the drug blood levels and dose related adverse effects, multiple dosing also fails to release the drug at the desired rate and in the desired amount which often results in poor patient compliance and inefficient therapy (Allison et al., 1992).

Solid Dispersions (SDs) are resulted by dispersion of drug in biologically inert matrix. They can be used to increase the solubility of a drug with low aqueous solubility, thereby improving its oral bioavailability. Higher drug dissolution rates from a SD can be facilitated by optimizing the wetting characteristics of the compound surface, as well as increasing the interfacial area available for drug dissolution. Although the latter can be easily accomplished by, for example, decreasing the particle size of the drug powder but micronized powders may result in further complications as they occasionally tend to agglomerate. A more preferable solution would be to introduce the drug in the form of a molecular dispersion (Nikghalb et al., 2012).

The mechanisms of enhancement of dissolution rate of SDs have been proposed by several investigators. A molecular dispersion of the drug in polymeric carriers

may lead to particle size reduction and surface area enlargement, which results in improved dissolution rates. Furthermore, no energy is required to break up the crystal lattice of a drug during the dissolution process, and there is an improvement in drug solubility and wettability due to surrounding hydrophilic carriers (Amte et al., 2012; Almeida et al., 2012; Singh et al., 2012).

The aim of the present study was to develop controlled release oral product namely solid dispersion of ketorolac using Eudragit RS100, Eudragit RL 100 and ethyl cellulose as coating materials in different proportions (1:1, 1:2 and 1:3) drug-polymer ratios. Investigation of the effect of various processing and formulation factors such as drug to polymer ratio, nature of polymer on the yield production, flowability of the product , in-vitro release rate of the drug from the obtained solid dispersion, stability study, release kinetics were performed. The possibility of the presence of interaction between the drug and polymers was determined by infrared spectral analysis (IR), differential thermal analysis (DTA) and X- ray diffraction.

MATERIALS AND METHODS

Materials

Ketorolac tromethamine (Sigma- Aldrich, St. Louis, Mo, USA) was a gift sample kindly supplied by Amriya pharmaceuticals industries, Alexandria, Egypt, Eudragit RL100 and Eudragit RS 100 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 with Eudragit RL100, Eudragit RS100 and Ethyl cellulose (in ratios of 1:1, 1:2 and 1:3) drug to polymer were prepared. The content of each formula is illustrated in Table (1).

Table 1: The ratios used in solid dispersion

Ratio	Ketorolac (mg)	Chosen Polymer (mg)
1:1	50	50
1:2	50	100
1:3	50	150

The method was achieved by dissolving the calculated amount of the polymer in a mixture of ethanol: dichloro methane in a ratio (1:1) in a glass vessel at 40° 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 obtained mixture was used as a solvent for the used polymers. The calculated amount 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 at room temperature. The dry film obtained was pulverized and passed through No 450µm sieve in order to obtain a homogenous particle size (Sera juddin, 1999; Rassu et al., 2008; Sudhamani et al., 2010). The obtained product was kept in a desiccator over silica gel under reduced pressure until used.

Infrared spectral analysis

The IR spectrum was used to determine the interaction of the drug with the polymers used. The infrared spectra of samples were obtained using a spectrophotometer (FTIR, Jusco, Japan). Samples were mixed with potassium bromide (spectroscopic grade) and compressed into discs using hydraulic press before scanning from 4000 to 400 cm^{-1} (Dyer, 1989).

Differential Thermal Analysis (DTA)

The physical state of drug in the solid dispersion was analyzed by Differential Thermal Analyzer (Mettler-Toledo star 822e system, Switzerland). The thermograms of the samples were obtained at a scanning rate of 10°C/min conducted over a temperature range of 25-220°C, respectively (Pignatello et al., 2001).

X-ray Diffractometry (XRD)

X-ray Diffractometry of ketorolac solid dispersion were performed by a diffractometer using model (Joel JDX-8030, Japan) equipped with a graphite crystal monochromator (Cu-Kα) radiations to observe the physical state of drug in the solid dispersion (Pignatello et al., 2001).

Micrometric properties

Flowability testing

The flowability of the prepared mixtures was tested by measuring their angle of repose as well as the calculation of Carr's compressibility index.

Measuring the angle of repose

The fixed height cone method was adopted (Luner et al., 2001) where the diameter of the formed cone (d) was determined according to the following equation:

$$\mathbf{Tan\ \theta = \frac{2h}{d}}$$

Where (h) and (d) are the height and the diameter of the cone respectively

Determination of Carr's compressibility index

A fixed weight of the powder either drug alone or in the prepared mixtures was poured into a 25 ml graduated cylinder, the mixture was allowed to settle with no outer force and the volume occupied was measured as V_I (initial bulk volume).The graduated cylindrical was then tapped on a plan surface at a one inch distance

till a constant volume was obtained . The tapped volume of the powder was then recorded as (V_T). The initial and tapped bulk densities were then calculated according to the following equation:

$$\text{Initial Bulk Density} \quad \rho_I = \frac{M}{VI}$$

$$\text{Tapped Bulk Density} \quad \rho_T = \frac{M}{VT}$$

Where (M) is the mass of the powder

The percentage compressibility (Carr's index) was then determined from the following equation:

$$\text{Carr's index} = \frac{\rho T - \rho I}{\rho T}$$

Finally the Hausner's ratio was obtained by dividing V_I by V_T **(Carr,1964)**.The experiments were carried in triplicate and the average angle of repose ,Carr's index and Hausner's ratio of each of the prepared formulae were then calculated as mean ± SD.

Drug content determination

Percentage yield was determined by calculating the initial weight of raw materials and the finally obtained weight of solid dispersion. Percentage yield was calculated by using the formula:

$$\text{Percentage yield} = \frac{\text{Percentage yield}}{\text{Theoritical yield}} \times 100$$

Accurately weighed amounts were taken in a stoppered test tube and extracted with 5×10 ml quantities of phosphate buffer pH 7.4.The extracts were filtered through 0.45 membrane filter and collected into 100 ml of volumetric flask and made up to the volume with phosphate buffer (pH 7.4). The solutions were subsequently diluted suitably with phosphate buffer (pH 7.4) and spectrophotometric absorbance was recorded at 323 nm (Sinha et al., 2009) (UV-Visible recording spectrophotometer, SHIMADZU (UV-160A) (Japan)). Percentage drug entrapment and the percentage entrapment efficiency (PEE) were calculated by the formula given below (Viral et al., 2010; John and Harinath, 2008; Ali et al., 2005). The drug content was performed in triplicate for each sample and the results were reported as mean ± SD.

$$\text{PEE} = \frac{\text{Drug loading solid dispersion}}{\text{Theoritical drug loading}} \times 100$$

In-vitro drug release studies

The release rate of ketorolac solid dispersion was studied using USP dissolution test apparatus employing paddle type (Paddle type , Copley , England). Accurately weighed samples of the prepared formulations were used which were calculated to contain 10 mg of the tested drug. Samples were placed in 900 ml of dissolution media (two types pH 1.0, 0.1 N HCl and pH 7.4 phosphate buffer). Paddle speed of 100 rpm at a temperature of 37.5°C ± 0.2 was employed. Aliquots (5ml) were withdrawn , filtered through 0.45 membrane filter at (5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes) at pH 1.0 and samples (5ml) were taken at predetermined time intervals for a period of 12 hours (0.50, 0.75, 1.0, 1.50, 2.0, 4.0, 6.0, 8.0, 10.0 and 12.0 hours) at pH 7.4. The withdrawn samples replaced with equal volumes of pre warmed fresh medium to maintain constant volume and keep sink condition. The drug concentration and the percentage drug released were determined spectrophotometrically at 323 nm with respect to time **(Raval et al., 2010)**. The in-vitro dissolution studies were performed in triplicate for each sample and the results were reported as mean ± SD.

Stability study

A stability test was conducted by storing the prepared formulations in amber glass bottles at ambient temperature, 31, 37, 43°C (the relative humidity was controlled at 75%, except at ambient temperature). The content of ketorolac as well as the release of drug from the proposed formulations were tested monthly along a period of six months. The dissolution study of the tested formulations was performed following the same procedures as previously described (Goudanavar et al., 2010).

Statistical analysis

ANOVA test was used to compare between the percentage released of the drug measured after in vitro release studies in 0.1 N HCl (pH 1.0) and phosphate buffer at pH of 7.4 in the case of solid dispersion formulations with the corresponding free drug to determine whether there were significant differences in between or not.

Kinetics of drug release

In order to determine the mechanism and kinetics of drug release, the drug release data of the in-vitro dissolution study was analyzed with various kinetic equations zero-order (% drug released v/s time), first order (Log % drug remaining v/s time) and Higuchi (% drug released v/s square root of time). Coefficient of correlation (r^2) values were calculated for the linear curves obtained by regression analysis of the above plots.

RESULTS AND DISCUSSION

Infrared spectral analysis

Infrared studies (Figures 1-a, 1-b, 1-c and 1-d) reveal that there is no appearance of new peaks and disappearance of existing peaks, which indicated that there is no interaction between the drug and the polymers used.

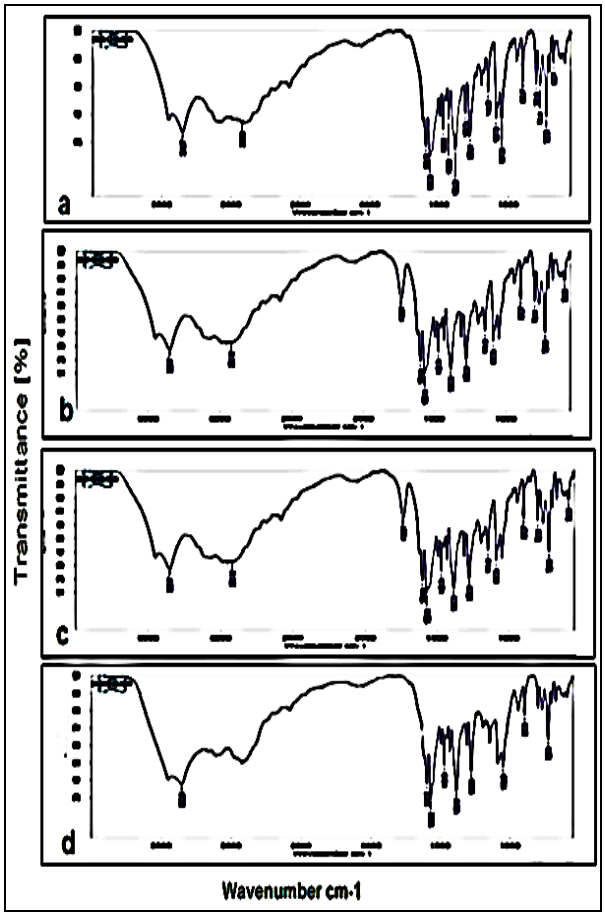

Figure 1: IR spectra of free drug (a), ketorolac with Eudragit RS100 (b), ketorolac with Eudragit RL100 (c) and ketorolac with Ethyl cellulose (d)

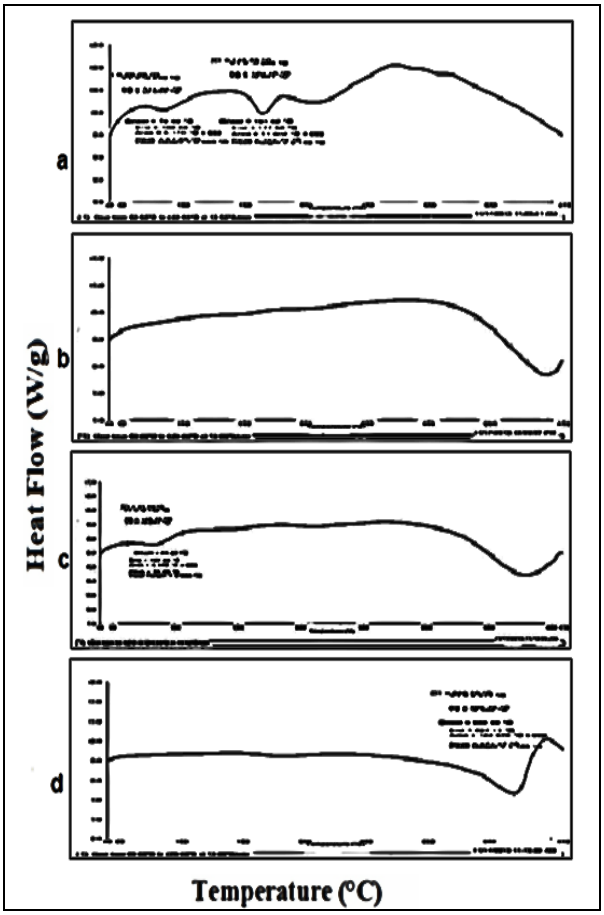

Figure 2: DTA thermogram of free drug (a), ketorolac with Eudragit RS100 (b), ketorolac with Eudragit RL100 (c) and ketorolac with Ethyl cellulose (d)

The IR spectrum of ketorolac tromethamine exhibited peaks at 3350.01cm^{-1} due to N-H and NH2 stretching and peaks at 1469.43 cm^{-1} and 1430.88 cm^{-1} due to C=C 1469.43 cm^{-1} and 1430.88 cm^{-1} due to C=C aromatic and aliphatic stretching, on the other hand, peak at1383.19cm^{-1} is due to-C-N vibrations, peak at 1047.59 cm^{-1} is due to -OH bending which confirms the presence of alcoholic group. Peaks at 702.09 cm^{-1}, 725.54 cm^{-1},771.71 cm^{-1} and 798.11 cm^{-1} confirm C-H bending (Aromatic), thus confirms the structure of ketorolac tromethamine.

IR studies show no interaction between drug and excipients. Additional peaks were absorbed in solid dispersion which could be due to the presence of polymers and indicated that there was no chemical interaction between ketorolac and other excipients. The spectra showed no incompatibility between the polymers and ketorolac. The spectra of the polymers and the free drug are given in the figures (1-a, 1-b, 1-c and 1-d).

Differential Thermal Analysis (DTA)

In order to confirm the physical state of the drug in the solid dispersion, DTA of the drug alone, and drug loaded microspheres were carried out (Fig 2-a, 2-b, 2-c and 2-d).

The DTA trace of drug showed a sharp endothermic peak at 168.88°C, its melting point. The physical mixture of drug and polymers used showed the same thermal behavior 168.76°C as the individual component, indicating that there was no interaction between the drug and the polymer in the solid state. The absence of endothermic peak of the drug at 168.88°C in the DTA of the drug loaded solid dispersion suggests that the drug existed in an amorphous or disordered crystalline phase as a molecular dispersion in a polymeric matrix (Zidan et al., 2006; Corrigan, 1995).

X-ray diffractometry (XRD)

In order to confirm the physical state of the drug in the solid dispersion, powder X-ray diffraction studies (George and Abraham, 2006) of the drug alone and drug loaded solid dispersion were carried out (Fig. 3-a, 3-b, 3-c and 3d).

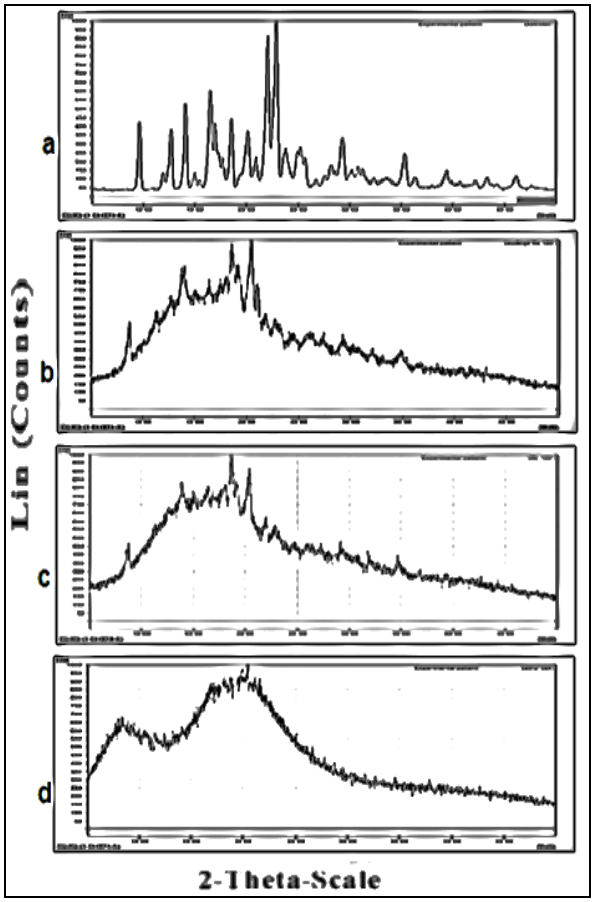

Figure 3: x-ray diffractogram of free drug (a), ketorolac with Eudragit RS100 (b), ketorolac with Eudragit RL100 (c) and ketorolac with Ethyl cellulose (d)

X-ray diffractograms of the samples showed that the drug is completely amorphous inside the solid dispersion. This may be due to the conditions used to prepare the microspheres lead to cause complete drug amorphization.

Micrometric Parameters

The effect of presence of ketorolac in solid dispersion systems on the flow properties of the drug is illustrated in Table (2).

Table (2) Micrometric properties of ketorolac and its solid dispersion form

Where:

Parameter	Free drug	Drug- Eudragit RS100 solid dispersion			Drug- Eudragit RL100 solid dispersion			Drug- Ethyl cellulose solid dispersion		
-	Drug- polymer ratio									
	-	1:1	1:2	1:3	1:1	1:2	1:3	1:1	1:2	1:3
P_T/P_I	2.14	1.22	1.15	1.08	1.21	1.19	1.16	1.29	1.28	1.20
Carr's index (%)	52.38	18.18	13.04	7.61	17.50	16.00	12.90	22.35	22.22	16.67
Angle of repose	58	33	28	22	20	26	35	38	30	25

P_I: Initial bulk density.
P_T: Tapped bulk density.
P_T / P_I: Hausner ratio.

Table (2) shows the results of the flowablity testing of ketorolac as well as the drug in the solud dispersion mixture with Eudragit RS100, Eudragit RL100 and ethyl cellulose it is clear that; Hausner's ratio of the drug alone was found to be 2.14 which indicates a poor flow property . The solid dispersions based on Eudragit RS 100 showed a ratio between 1.08 and 1.22, while those based on Eudragit RL100 revealed a ratio between 1.16 and 1.19, also, those based on Ethyl cellulose showed a ratio between 1.20 and 1.29 indicating a good flow (Yanbin et al., 2006).

Carr's index for the drug alone was found to be 52.38 % indicating extremely poor flow. The solid dispersions based on Eudragit RS 100 showed an index between 7.61 and 13.04 % ,while those based on Eudragit RL100 showed an index between 12.90 and 17.50 %, on the other hand, those based on Ethyl cellulose showed an index between 16.67and 22.22 % indicating excellent and good flow **(Yanbin et al., 2006)**.

In all formulations the ratio 1:3 drug to polymer showed the best flowability results. It is evident from Table (2) that the angle of repose decreases by inclusion of the drug in a solid dispersion system, also by increasing the ratio of the polymers, the angle of repose decreases i.e. flowability increases.

Ketorolac content determination

Ketorolac content in different solid dispersion formulations ranges between 96.45 and 102.20%. Table (3) summarizes the ketorolac content in its different solid dispersions formulations.

Table (3): Ketorolac content in different solid dispersion formulations

Polymers used	Drug: polymer ratio	(%) Ketorolac content*
Eudragit RS100	1:1	98.30±1.21
	1:2	99.55±1.89
	1:3	99.95±1.30
Eudragit RL100	1:1	102.20±1.45
	1:2	98.74±1.81
	1:3	96.49±1.32
Ethyl cellulose	1:1	101.80±2.27
	1:2	99.12±1.48
	1:3	100.00±1.35

***(Mean ± SD, n=3)**.

Table (3) shows the results of ketorolac content in different solid dispersions formulations, it is clear that the percentage yield of different solid dispersion formulations varied from 96.45 to 102.20. From the obtained results in the table it is evident that drug to polymer ratio did not play any rule in the drug content of the drug. This is in contrast to the results obtained by **(Trivedi et al., 2008)** who reported that by increasing the polymer ratio in certain formulations from 1:1 to 1:5 was followed by increasing the drug entrapment efficiency.

Swetha et al., 2011 prepared micro sponges containing etodolac with different types of polymers including Eudragit and Ethyl cellulose. The authors proved that the ratio of the polymer in the delivery system has no effect on the percentage entrapment efficiency.

Zien et al., 2015 prepared solid dispersion containing diclofenac with different types of polymers including Eudragit RS 100, Eudragit RL 100 and Ethyl cellulose. The authors proved that the ratio of the polymer in the delivery system has no effect on the percentage entrapment efficiency.

In-vitro drug release studies

The release profiles of ketorolac solid dispersion systems from different solid dispersion systems. Various ratios of drug to polymer at different pH values are shown in Figures (4-6).

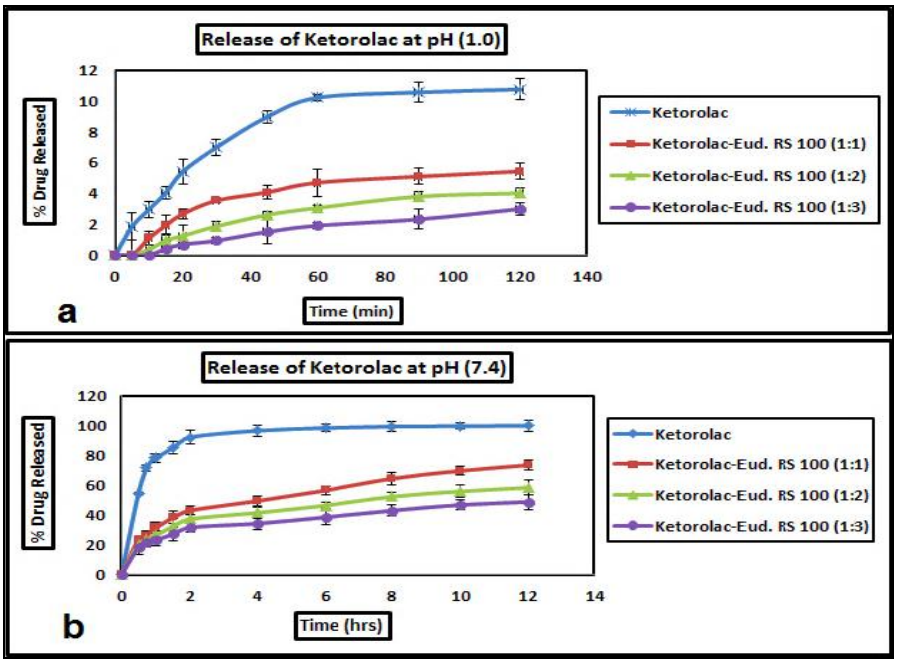

Fig (4): Release of ketorolac from its solid dispersions with Eud. RS100 at pH 1.0 (4-a) and pH 7.4 (4-b) in a drug to polymer ratios of (1:1, 1:2 & 1:3)

A poor drug release ranging from 1.85±0.32 to 10.76±0.75 was observed from the solid dispersion systems in pH 1.0 by the end of 2 h of dissolution. This can be attributed to the pH dependent solubility of the drug, which is reported to increase at pH values higher than the pK_a (4.0) of the drug **(Ammar and Khalil, 1997)**.

From Figure (4) it is obvious that, the drug release from the solid dispersions in pH 7.4 is dependent on the total polymer levels. Solid dispersions produced with Eudragit

RS showed slow drug release ranging from 48.72±1.45% to73.41±1.07% by the end of 12 h of dissolution at low and high polymer levels respectively. The amount of the drug released was inversely proportional to the polymer ratio in the solid dispersion systems.

At pH 1.0, the percentage of drug released after 120 minutes from Eudragit RS100 solid dispersion system at drug to polymer ratio of (1:1) was decreased significantly (p value < 0.5) than free drug at the same pH this is because Eudragit RS100 does not dissolve in acidic pH.

At pH of 7.4, the percentage of drug released after 12 hours from Eudragit RS100 solid dispersion system at drug: polymer ratio of (1:1) showed significant decrease in percentage released of ketorolac than drug alone at the same pH (p value < 0.5).

By increasing the ratio of the polymer there was a decrease in the percentage ketorolac released at low pH values of 1.0 to reach (1:2) drug to polymer ratio, the obtained results showed that, at pH 1.0, the percentage of drug released after 120 minutes from Eudragit RS100 solid dispersion system at drug to polymer ratio of (1:2) was decreased significantly (p value < 0.5) than free drug at the same pH, and also significant (p value < 0.5) than that of ketorolac in Eudragit RS100 solid dispersion system in the ratio of (1:1).

At pH of 7.4, the percentage of drug released after 12 hours from Eudragit RS100 solid dispersion system at drug to polymer ratio of (1:2) was decreased significantly (p value < 0.5) than free drug at the same pH, but not significant (p value > 0.5) than that of ketorolac in Eudragit RS100 solid dispersion system in the ratio of (1:1).

By increasing the ratio of the polymer to decrease the percentage of drug released at low pH values of 1.0 to reach (1:3) drug to polymer ratio, the obtained results showed that, at pH 1.0, the percentage of drug released after 120 minutes from Eudragit RS100 solid dispersion system at drug to polymer ratio of (1:3) was decreased significantly (p value < 0.5) than free drug at the same pH, and also significant (p value < 0.5) than that of ketorolac in Eudragit RS100 solid dispersion system in the ratios of (1:1) & (1:2) respectively.

At pH of 7.4, the percentage of drug released after 12 hours from Eudragit RS100 solid dispersion system at drug to polymer ratio of (1:3) was decreased significantly (p value < 0.5) than free drug, and also significant (p value < 0.5) than that of ketorolac in Eudragit RS100 solid dispersion systems in the ratios of (1:1) & (1:2) respectively at the same pH.

The slow drug release from solid dispersions with Eudragit RS can be attributed to the low permeability of the polymer, which posed a significant hindrance to fluid penetration and passive drug diffusion.

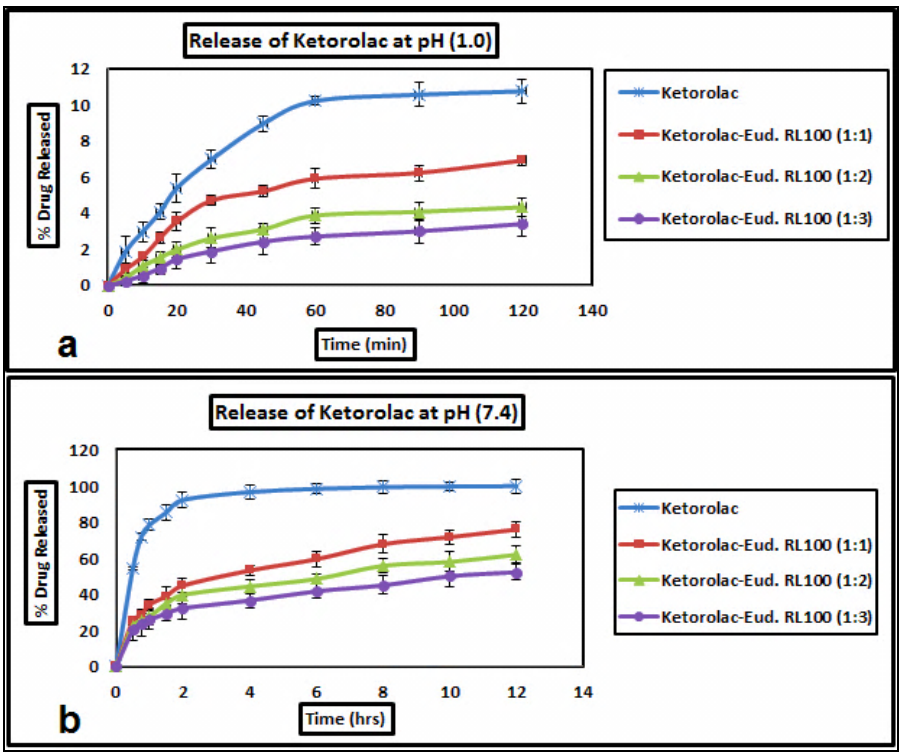

Fig (5): Release of ketorolac from its solid dispersions with Eud. RL100 at pH 1.0 (5-a) and pH 7.4 (5-b) in a drug to polymer ratios of (1:1, 1:2 & 1:3)

Incorporation of the drug in a solid dispersion system with Eudragit RL is reported to enhance the drug release from the solid dispersion **(Jenquin et al., 1990)**. The drug release from the solid dispersions in pH 7.4 was dependent on the total polymer levels. Solid dispersions prepared with Eudragit RL showed slow drug release ranging from 52.18±1.22% to75.76±0.72% by the end of 12 hours of dissolution at low and high polymer levels respectively. The amount of the drug released was inversely proportional to the polymer ratio in the solid dispersion systems.

From Figure (5) it is obvious that, at pH 1.0, the percentage of drug released after 120 minutes from Eudragit RL100 solid dispersion system at drug to polymer ratio of (1:1) was decreased significantly (p value < 0.5) than free drug at the same pH this is because Eudragit RL100 does not dissolve in acidic pH.

At pH of 7.4, the percentage of drug released after 12 hours from Eudragit RL100 solid dispersion system at drug to polymer ratio of (1:1) showed significant decrease in percentage released of diclofenac than free drug at the same pH (p value < 0.5).

By increasing the ratio of the polymer a decrease in the amount of drug was observed at low pH values of 1.0 to reach (1:2) drug: polymer ratio, the obtained results showed that, at pH 1.0, the percentage released after 120 minutes of ketorolac in Eudragit RL100 solid dispersion system at drug to polymer ratio of (1:2) was decreased significantly (p value < 0.5) than drug alone at the same pH, but not significant (p value > 0.5) than that of ketorolac in Eudragit RL100 solid dispersion system (1:1).

At pH of 7.4, the percentage of drug released after 12 hours from Eudragit RL100 solid dispersion system at drug to polymer ratio of (1:2) was decreased significantly (p value < 0.5) than free drug at the same pH, but not significant (p value > 0.5) than that of ketorolac in Eudragit RL100 solid dispersion system (1:1).

By increasing the ratio of the polymer a decrease in the amount of drug was observed at low pH values of 1.0 to reach (1:3) drug to polymer ratio, the obtained results showed that, at pH 1.0, the percentage released after 120 minutes of ketorolac in Eudragit RL100 solid dispersion system at drug to polymer ratio of (1:3) was decreased significantly (p value < 0.5) than drug alone at the same pH, and also significant (p value < 0.5) than that of ketorolac in Eudragit RL100 solid dispersion system in the ratios of (1:1) & (1:2) respectively.

At pH of 7.4, the percentage released after 12 hours of ketorolac in Eudragit RL100 solid dispersion system at drug to polymer ratio of (1:3) was decreased significantly (p value < 0.5) than free drug, and also significant (p value < 0.5) than that of ketorolac in Eudragit RL100 solid dispersion systems in the ratios of (1:1) & (1:2) respectively at the same pH.

This increase in percentage released compared with Eudragit RS was due to increased permeability and hydrophilicity of Eudragit RL because of the higher content of quaternary ammonium group in Eudragit RL.

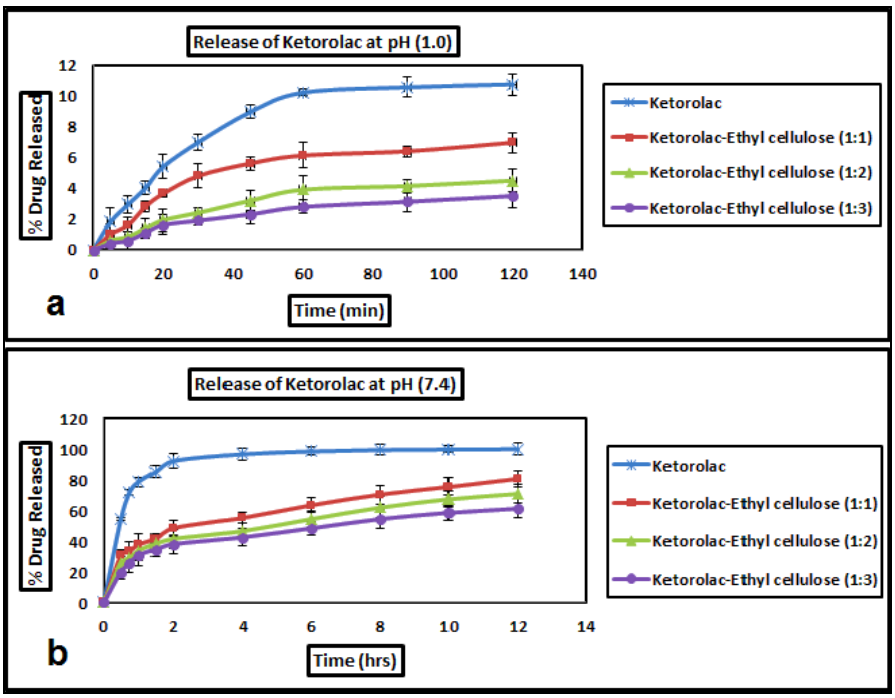

Fig (6): Release of ketorolac from its solid dispersions with E.C at pH 1.0 (6-a) and pH 7.4 (6-b) in a drug to polymer ratios of (1:1, 1:2 & 1:3)

From Figure (6) it is obvious that, the drug release from the solid dispersions in pH 7.4 was dependent on the total polymer levels. Solid dispersions produced with Ethyl cellulose showed slow drug release ranging from 60.33±0.98% to74.22±0.11% by the end of 12 hours of dissolution at low and high polymer levels respectively. The amount of the drug released was inversely proportional to the polymer ratio in the solid dispersion systems .This may be due to increase in system viscosity with increase in Ethyl cellulose concentration **(Sajeev et al., 2002; Biju et al., 2004)**.

At pH 1.0, the percentage of drug released after 120 minutes from Ethyl cellulose solid dispersion system at drug to polymer ratio of (1:1) was decreased significantly (p value < 0.5) than free drug at the same pH, this because Ethyl cellulose does not dissolve in acidic pH.

At pH of 7.4, the percentage of drug released after 12 hours from Ethyl cellulose solid dispersion system at drug to polymer ratio of (1:1) showed non-significant decrease in percentage released of ketorolac than free drug at the same pH (p value > 0.5).

By increasing the ratio of the polymer a decrease in the amount of drug was observed at low pH values of 1.0 to reach (1:2) drug to polymer ratio, the obtained results showed that, at pH 1.0, the percentage of drug released after 120 minutes from Ethyl cellulose solid dispersion system at drug to polymer ratio of (1:2) was decreased significantly (p value < 0.5) than free drug at the same pH, and also significant (p value < 0.5) than that of ketorolac in Ethyl cellulose solid dispersion system in the ratio of (1:1).

At pH of 7.4, the percentage released after 12 hours of ketorolac in Ethyl cellulose solid dispersion system at drug to polymer ratio of (1:2) was decreased significantly (p value < 0.5) than free drug at the same pH, but not significant (p value > 0.5) than that of ketorolac in Ethyl cellulose solid dispersion system in the ratio of (1:1).

By increasing the ratio of the polymer a decrease in the amount of drug was observed at low pH values of 1.0 to reach (1:3) drug to polymer ratio, the obtained results showed that, at pH 1.0, the percentage of drug released after 120 minutes from Ethyl cellulose solid dispersion system at drug: polymer ratio of (1:3) was decreased significantly (p value < 0.5) than free drug at the same pH, and also significant (p value < 0.5) than that of ketorolac in Ethyl cellulose solid dispersion system in the ratio of (1:1) but not significant (p value > 0.5) than that of ketorolac in Ethyl cellulose solid dispersion system in the ratio of (1:2) at the same pH.

At pH of 7.4, the percentage of drug released after 12 hours from Ethyl cellulose solid dispersion system at drug to polymer ratio of (1:3) was decreased significantly (p value < 0.5) than free drug, and also significant (p value < 0.5) than that of ketorolac in Ethyl cellulose solid dispersion systems in the ratios of (1:1) & (1:2) respectively at the same pH.

Screening the previous results of drug release from Eudragit RS100, Eudragit RL100 and Ethyl cellulose solid dispersion systems in all ratios of (1:1, 1:2 & 1:3) at different pH values of 1.0 and 7.4, It was found that Eudragit RS100, Eudragit RL100 and Ethyl cellulose have better enteric properties especially at a ratio of (1:3). This indicates that Eudragit RS100, Eudragit RL100 and Ethyl cellulose have sufficient thickness and uniformity to prevent drug release in the gastric fluid, so that, these polymers are capable of protecting the drug in a better manner, also, increase in the drug to polymer ratios accounted for significant difference in decreasing the amount of drug released especially at low pH values of stomach.

For enteric polymers as Eudragit RS100, Eudragit RL100 and Ethyl cellulose at drug to polymer ratio of (1:1), the polymer is unable to coat the drug completely. By increasing the drug to polymer ratio to (1:3), Eudragit RS100, Eudragit RL100 and Ethyl cellulose showed significant decrease in drug release measured by percentage released after 120 minutes of ketorolac from Eudragit RS100, Eudragit RL100 and Ethyl cellulose solid dispersion systems than (p value < 0.5) than free drug at the stomach pH.

There was no significant decrease in drug release from Eudragit RS100, Eudragit RL100 and Ethyl cellulose at alkaline pH of the intestine (p value > 0.5).

Stability test

Table (4) shows the release profile of ketorolac from three different batches constructed, it is clear that there was no significant difference among the release profile for each set of the three batches along the storage period, indicating that this manufacturing process is reliable and reproducible. The table shows stability of ketorolac in different prepared formulations giving the percentage remaining of the drug in the formulation**.**

Table (4): Stability of ketorolac in different prepared formulations

Polymers used	Drug: polymer ratio	Time (Months)		
		1	3	6
Eudragit RS 100	1:1	98.45±0.22	97.54±0.34	96.82±1.00
	1:2	99.12±1.07	98.40±0.38	97.88±0.54
	1:3	97.89±0.45	96.56±1.01	95.56±0.76
Eudragit RL 100	1:1	99.00±0.34	98.42±0.67	97.70±1.55

	1:2	97.98±0.67	96.17±0.65	95.78±0.23
	1:3	99.88±1.54	98.67±0.40	97.56±1.33
Ethyl cellulose	1:1	98.12±0.87	97.69±0.45	96.34±0.90
	1:2	99.85±1.00	98.67±1.98	97.78±1.46
	1:3	97.58±0.22	96.18±0.78	95.54±1.98

From the Table, the stability of ketorolac in these formulations was examined over six months. There was insignificant ketorolac degradation in the prepared formulations. Apparently, the release of the drug from all formulations didn't change after storage at all temperature utilized for this period of time, suggesting that ketorolac is stable in the chosen matrices and the controlled release ability of these matrices is not influenced by the temperature range tested.

Kinetic analysis of the release of ketorolac

Table 5 and 6 show the mechanism of release kinetic of ketorolac from different controlled release formulations in 0.1 NHCl (pH 1.0) and in phosphate buffer (pH 7.4).

Table (5): In vitro release characteristics of ketorolac from its solid dispersions systems in 0.1 N HCl

Formula	Drug: Polymer Ratio	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Release Mechanism	K
Ketorolac	Free drug	0.9325	**0.9919**	0.9661	First	0.0004±0.002
Ketorolac-Eud.RS100	1:1	0.9159	0.9807	0.9903	Higuchi	1.22±0.980
	1:2	0.9469	0.9611	0.9931	Higuchi	2.21±0.328
	1:3	0.9591	0.9647	0.9981	Higuchi	1.65±0.310
Ketorolac-Eud.RL100	1:1	0.9639	0.9823	0.9975	Higuchi	2.23±0.031
	1:2	0.9541	0.9656	0.9984	Higuchi	4.12±0.087
	1:3	0.9605	0.9857	0.9957	Higuchi	9.62±0.044
Ketorolac-Ethyl Cellulose	1:1	0.9416	0.9914	0.9988	Higuchi	6.10±0.130
	1:2	0.9542	0.9791	0.9953	Higuchi	3.54±0.340
	1:3	0.9961	0.9969	0.9993	Higuchi	5.32±0.087

Data are mean ± SD; K is the release rate constant

Table (6): In vitro release characteristics of ketorolac from its solid dispersions systems in phosphate buffer (pH 7.4)

Formula	Drug: Polymer Ratio	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Release Mechanism	K
Ketorolac	Free drug	0.9288	**0.99**97	0.9724	First	0.007±0.0002
Ketorolac-Eud.RS100	1:1	0.9304	0.9839	0.9958	Higuchi	1.15±0.077
	1:2	0.9308	0.9657	0.9928	Higuchi	1.87±0.124
	1:3	0.9317	0.9184	0.9839	Higuchi	5.23±0.547
Ketorolac-Eud.RL100	1:1	0.9696	0.9742	0.9971	Higuchi	3.32±0.330
	1:2	0.9541	0.9656	**0.9984**	Higuchi	2.34±0.150
	1:3	0.9431	0.9895	**0.9965**	Higuchi	4.23±0.461
Ketorolac-Ethyl Cellulose	1:1	0.9758	0.9513	**0.9985**	Higuchi	2.90±0.540
	1:2	0.9225	0.9263	0.9913	Higuchi	3.31±0.220
	1:3	0.9753	0.9488	0.9942	Higuchi	1.12±0.679

Data are mean ± SD; K is the release rate constant

From tables (5& 6) it is obvious that.

The release kinetics of ketorolac free drug was best fitted to the first order model; on the other hand, the release kinetics of the formulations was checked by fitting the release data to various kinetic models. The release was best fitted to the Higuchi model. Higuchi equation explains the diffusion controlled release mechanism.

All the parameters were run 3 times (n=3). The difference in mean of Zero order, First order and Higuchi kinetics between different formulas "K" was indicating significant ($p < 0.05$).

CONCLUSION

Solid dispersion technique has been successfully employed to produce controlled release drug delivery for ketorolac. FT-IR studies revealed that there was no significant drug interactions between the drug and the polymers used. There was no significant degradation of ketorolac or change in drug release rate in any of the proposed formulations during a six-month period of stability testing. Ketorolac content in different formulations wasn't affected by neither the polymer type nor drug to polymer ratio. The formulations followed Higuchi model release kinetics. Therefore, one can

assume that the ketorolac solid dispersions are promising pharmaceutical dosage forms by providing controlled release drug delivery systems and avoiding the dose related side effects in the entire physiological region of the GIT. The entire process is feasible in an industrial scale and demands pilot study.

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