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DESIGN AND EVALUATION OF ENTERIC COATED FORMULATIONS FOR AN ANTI-INFLAMMATORY DRUG BASED ON MODIFIED RELEASE POLYMERS

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ABSTRACT

Ketorolac is a potent non-steroidal drug with potent analgesic and anti-inflammatory activity. Its oral administration is associated with a high risk of adverse effects such as irritation, ulceration and bleeding of gastrointestinal tract. The present study focuses on the development of controlled release drug delivery system of ketorolac microcapsules as one of the multi-particulate formulations and are prepared to obtain prolonged drug delivery in order to decrease ulcerogenicity, improve bioavailability or stability and target a drug at specific sites. Microcapsules were prepared using Eudragit RS100, Eudragit RL100 and ethyl cellulose in ratios of 1:1, 1:2 and 1:3 drug to polymer. IR, DTA and X-ray investigations revealed that there was no interaction between the drug and the polymers used. The *in-vitro* release studies showed that the release rate of the drug has been modified. This study presents a new approach based on microencapsulation technique for obtaining modified release drug delivery system.

KEYWORDS:

1- INTRODUCTION

Ketorolac is a potent non-steroidal analgesic drug, frequently used for treatment of rheumatoid arthritis, osteoarthritis, a variety of other acute and chronic musculoskeletal disorders and mild to moderate pain.[1-3] The drug acts as anti-inflammatory by inhibiting prostaglandin synthetase cyclooxygenase. It is 36 times more potent than phenyl butazone and twice as that of indomethacin.[4] Ketorolac is used clinically for the management of post-operative and cancer pain.

Previous studies have suggested that ketorolac's analgesic efficacy may be greater than other non-steroidal anti-inflammatory drug sand comparable with that of morphine in models of acute pain.[5-9]

Regardless of the route of administration, the biological half-life of the drug ranges from 4 to 6h in human[10], its oral bioavailability is estimated to be 80%. The oral administration of ketorolac is associated with high risk of adverse effects such as irritation, ulceration, bleeding of gastrointestinal tract, edema as well as peptic ulceration.[11] These attributes make ketorolac a good candidate for controlled release dosage form, so as to ensure slow release of the drug eliminating the disturbance of the gastrointestinal tract.

A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects. There are various approaches in delivery of a therapeutic substance to the target site in a controlled release fashion.[12, 13]

One such approach is using microcapsules as carriers for drugs. Microencapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsule. In a relatively simplistic form, a microcapsule is a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell coating or membrane. Most microcapsules have diameters ranging from less than one micron to several hundred microns in size.[14]

Acrylic resins and celluloses have been used to encapsulate drug particles and to obtain microcapsules with certain physicochemical properties and/or to alleviate certain side effects of the parent drug.[15-19]

Several types of acrylic resin polymers with distinct structures and properties were developed for coating.

These polymers, commercially available under the trade name Eudragits, are physiologically inert, resist enzymatic attack and are not absorbed by digestive tract. The cationic type Eudragit-E is soluble under weak acidic conditions and can be used for film coating or to isolate incompatible ingredients.[20]

The anionic types Eudragit-L and Eudragit-S are used as enteric coating agents and can be used to influence the dissolution rate of drugs in intestine. The permeable polymers, Eudragit retard-L and Eudragit retard-S are insoluble in the pH range of the digestive tract but swell in an aqueous medium and exhibit a distinct permeability for water as well as water soluble drugs. These permeable polymers are used in the formulation of controlled release medication. Ethyl cellulose is the ethyl ether of cellulose; it is mainly used either alone or with other polymers in formulations required for extended or controlled release.[21]

Microencapsulation technology involves a basic understanding of the general properties of microcapsules, including the nature of the core and coating material, the release characteristics of the coated particles and the method chosen for microencapsulation and also on the properties of the obtained microcapsules.[22]

The main objective of this work was to obtain controlled release ketorolac formulation by microencapsulation of the drug by the fluidized bed technique 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, *in-vitro* release rate of the drug from the obtained microcapsules were performed. The possibility of the presence of interaction between the drugs and polymers was determined by infrared spectral analysis (IR), differential thermal analysis (DTA) and X- ray.

2- MATERIALS AND METHODS

2.1. 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.

2.2. Coating of Ketorolac with Eudragit RS100, Eudragit RL 100 and Ethyl cellulose

2.2.1. Preparation of the coating solution

Coating solutions with concentration of 5% w/v Eudragit RS100, Eudragit RL 100 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.[23, 24]

2.2.2. 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 200ml. 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(µm)	(80-250)
Charged weight (gm.)	(30)

2.3. 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}.

2.4. Differential Thermal Analysis (DTA)
The physical state of drug in the microspheres was analyzed by Differential Thermal Analyzer (Mettler-Toledo star 822e system, Switzerland). The thermo grams of the samples were obtained at a scanning rate of 10°C/min conducted over a temperature range of 25-220°C, respectively.

2.5. X-ray Diffractometry (XRD)
X-ray Diffractometry of ketorolac microspheres 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 microspheres.

2.6. Scanning Electron Microscopy (SEM)
The shape and surface morphology of ketorolac loaded microspheres were studied using (Jeol, JSM-840A scanning electron microscope, Japan). The gold coated (thickness 200Å; Jeol, JFC-1100E sputter coater, Japan) microspheres were subjected to secondary imaging technique at 150 tilt,15mm working distance and 25 Kv accelerating voltage.

2.7. Drug content determination
Percentage yield can be determined by calculating the initial weight of raw materials and the finally obtained weight of microcapsules. Percentage yield can be calculated by using the formula.

$$\textbf{Percentage yield} = \frac{Practical\ yield}{Theoritical\ yield} \times \mathbf{100.}$$

Accurately weighed microcapsules were taken in a stoppered test tube and extracted with 5×10 ml quantities of phosphate buffer (pH7.4).The extracts were filtered and collected into 100 ml of volumetric flask and made up to the volume with phosphate buffer (pH7.4). The solutions were subsequently diluted suitably with pre warmed phosphate buffer (pH7.4) and spectrophotometric absorbance was recorded at 323nm.[25] (UV-Visible recording spectrophotometer, SHIMADZU (UV-160A) (Japan). Percentage drug entrapment and the percentage entrapment efficiency (PEE) were calculated by the formula given below.[26-28]

$$\textbf{PEE} = \frac{\textbf{Drug loading microcapsules}}{\textbf{Theoritical drug loading}} \times \mathbf{100}$$

2.8. *In-vitro* drug release studies:
The release rate of ketorolac microcapsules was studied using USP dissolution test apparatus employing paddle type (Paddle type, Copley, England). Accurately weighed samples of microcapsules were used which were calculated to contain 10 mg of the tested drug. They were placed in 900 ml of dissolution media (two types pH 1.0, 0.1 N HCL and pH 7.4 phosphate buffers). Paddle speed of 100 rpm and temperature of 37.5°C±0.2 was employed. Aliquots (5ml) were withdrawn, filtered through 0.45 membrane filter and replaced with equal volume of pre warmed fresh medium to maintain constant volume and keep sink condition.[29] The drug concentration and the percentage drug released were determined with respect to time spectrophotometrically at 323nm.[29] The *in-vitro* dissolution studies were performed in triplicate for each sample and the results were reported as mean ± SD.

2.9. Stability study
A stability test was conducted by storing the prepared formulation in amber 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 formulation were tested monthly for six months. The release study of the tested formulations followed the same procedures as previously described.[30]

2.10. Kinetics of drug release
In order to understand the mechanism and kinetics of drug release, the drug release data of the *in-vitro* dissolution study was analyzed with various kinetic equations like 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.

3-RESULTS AND DISCUSSION
3.1. Infrared spectral analysis
Infrared studies (Figures 1a, 1b, 1c and 1d) revealed 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.

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 microcapsules 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 pure drug are given in the figures (1-a, 1-b, 1-c and 1-d).

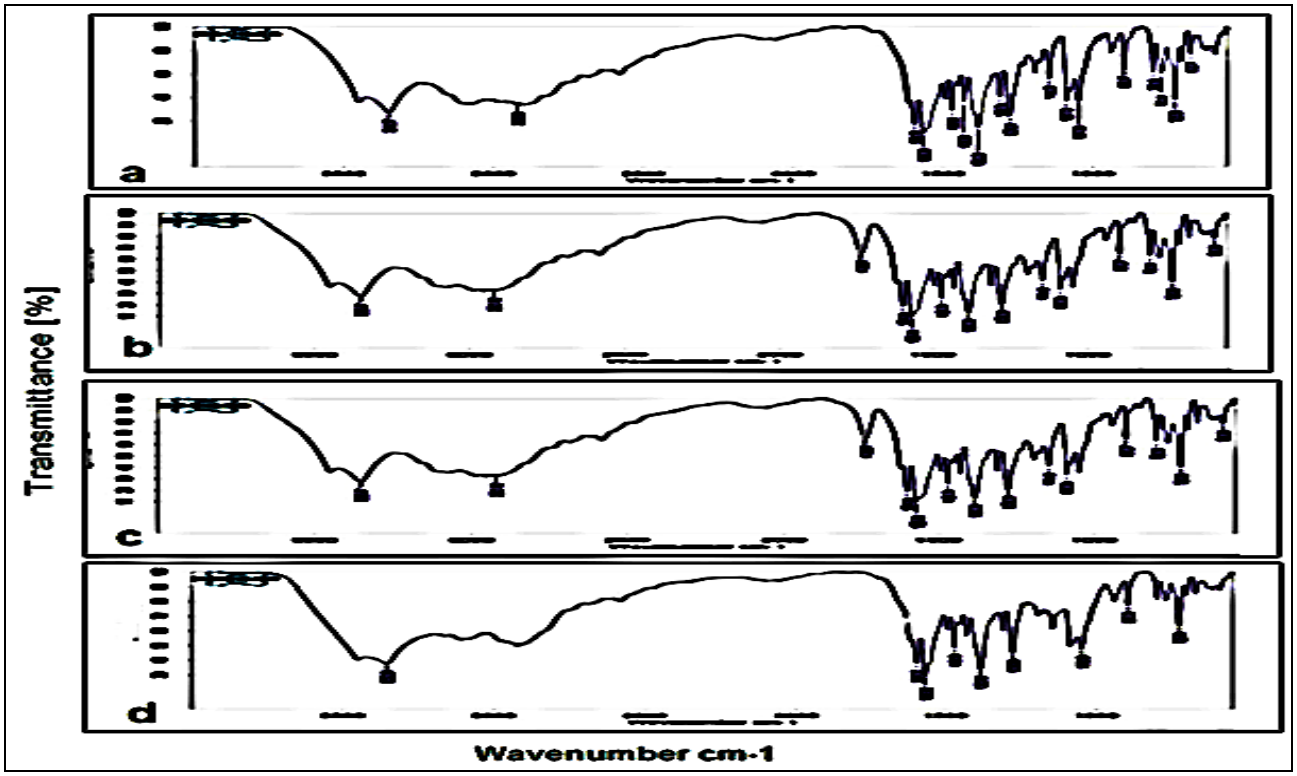

Figure 1: IR spectra of pure drug ketorolac (a), ketorolac coated with Eudragit RS100 (b), ketorolac coated with Eudragit RL100 (c) and ketorolac coated with Ethyl cellulose (d).

3.2. Differential Thermal Analysis (DTA)

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

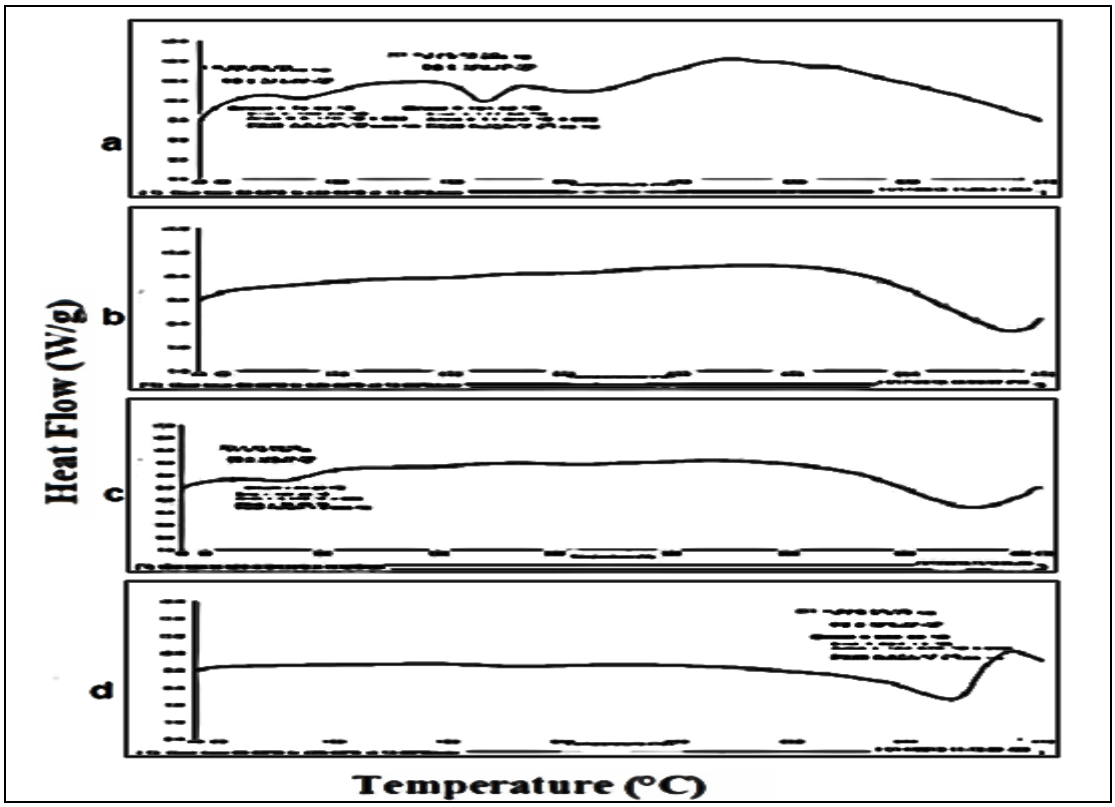

Figure 2: DTA thermogram of pure drug ketorolac (a), ketorolac coated with Eudragit RS100 (b), ketorolac coated with Eudragit RL100 (c) and ketorolac coated with Ethyl cellulose (d).

The DTA trace of drug showed a sharp endothermic peak at 168.88°C, its melting point. The physical mixture of drug and blank microspheres 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 microspheres suggests that the drug existed in an amorphous or disordered crystalline phase as a molecular dispersion in polymeric matrix.[31, 32]

3.3. X-ray diffractometry (XRD)

In order to confirm the physical state of the drug in the microspheres, powder X-ray diffraction studies.[33] of the drug alone and drug loaded microspheres were carried out(Fig. 3-a, 3-b, 3-c and 3d).

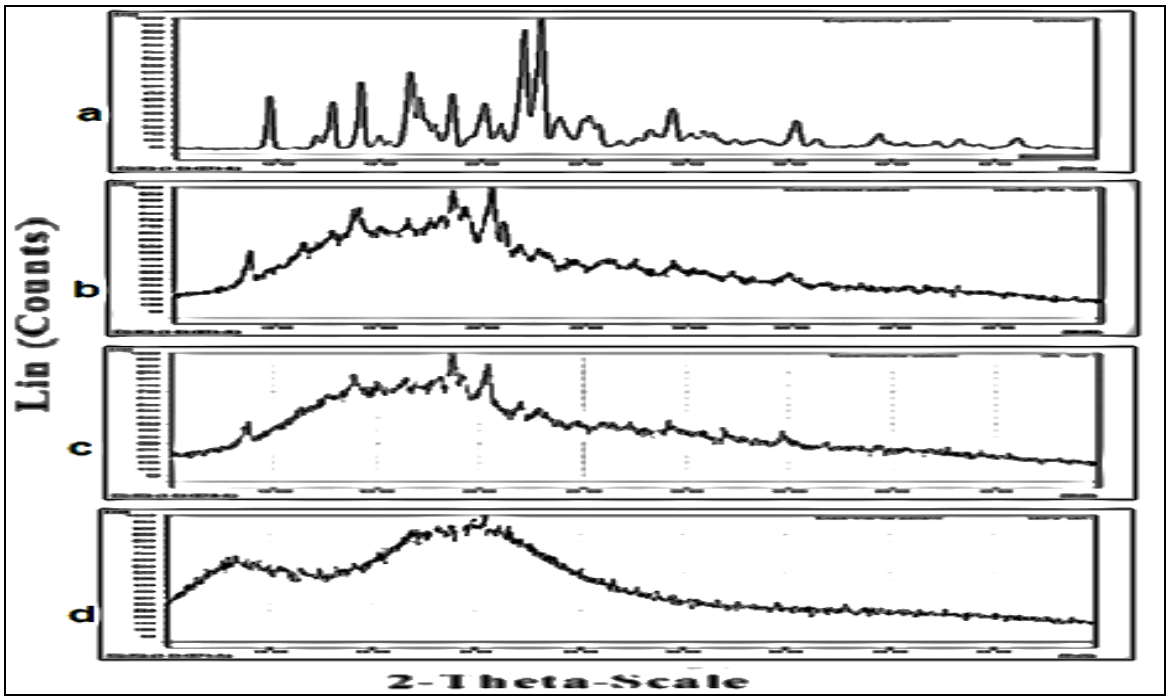

Figure 3: x-**ray diffractogram of pure drug ketorolac (a), ketorolac coated with Eudragit RS100 (b), ketorolac coated with Eudragit RL100 (c) and ketorolac coated with Ethyl cellulose (d).**

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

3.4. Scanning Electron Microscopy (SEM)

The surface morphology of the ketorolac and ketorolac loaded microspheres were studied by scanning electron microscopy (Fig. 4).

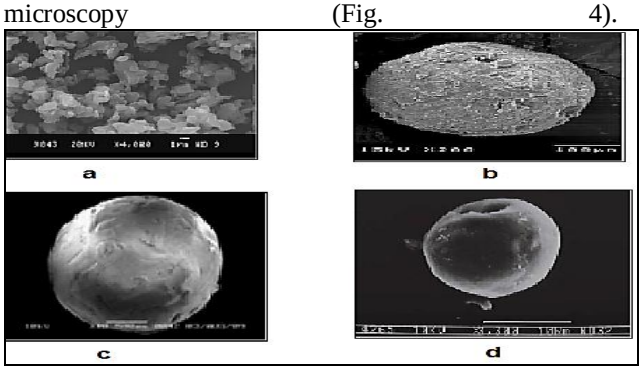

Figure (4): Scanning electron micrograph of ketorolac (a) ketorolac coated with Eudragit RS100 (b) ketorolac coated with Eudragit RL100(c) and ketorolac coated with Ethyl cellulose (d).

SEM photograph of the drug indicated that the drug exists in crystal form. Surface smoothness of MS was increased by increasing the polymer concentration, which was confirmed by SEM.

3.6. Drug content determination

Ketorolac content in different microcapsule formulations in phosphate buffer (pH7.4) is shown in Table (2).

Table (2): Ketorolac content in different microcapsule formulations in phosphate buffer (pH7.4).

Polymers used	Drug: polymer ratio	Ketorolac Content (%)
Eudragit RS 100	1:1	98.10 ± 2.30
	1:2	98.63 ± 1.72
	1:3	98.58 ± 1.16
Eudragit RL 100	1:1	99.10 ± 1.36
	1:2	99.67 ± 1.81
	1:3	98.73 ± 1.36
Ethyl cellulose	1:1	99.32 ± 1.23
	1:2	99.67 ± 1.96
	1:3	98.83 ± 1.21

(Mean ± SD, n=3).

Table (2) shows the results of ketorolac content in different microcapsule formulations, it is clear that the percentage yield of different microcapsule formulations varied from 98.10 ±2.30% to 99.67 ±1.81%. From the results in the Table it is evident that drug to polymer ratio did not play any rule in the entrapment efficiency of the drug. This is in contrast to the results obtained by Trivedi *et al*[34] who reported that by increasing the polymer ratio in certain formulations from 1:1 to1:5 was followed by increasing the drug entrapment efficiency.

Swetha *et al.*[35] 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.

3.7. *In-vitro* drug release studies

The release profile of ketorolac microcapsules prepared from different drug to polymer ratios at different values are shown in Figures (5-7).

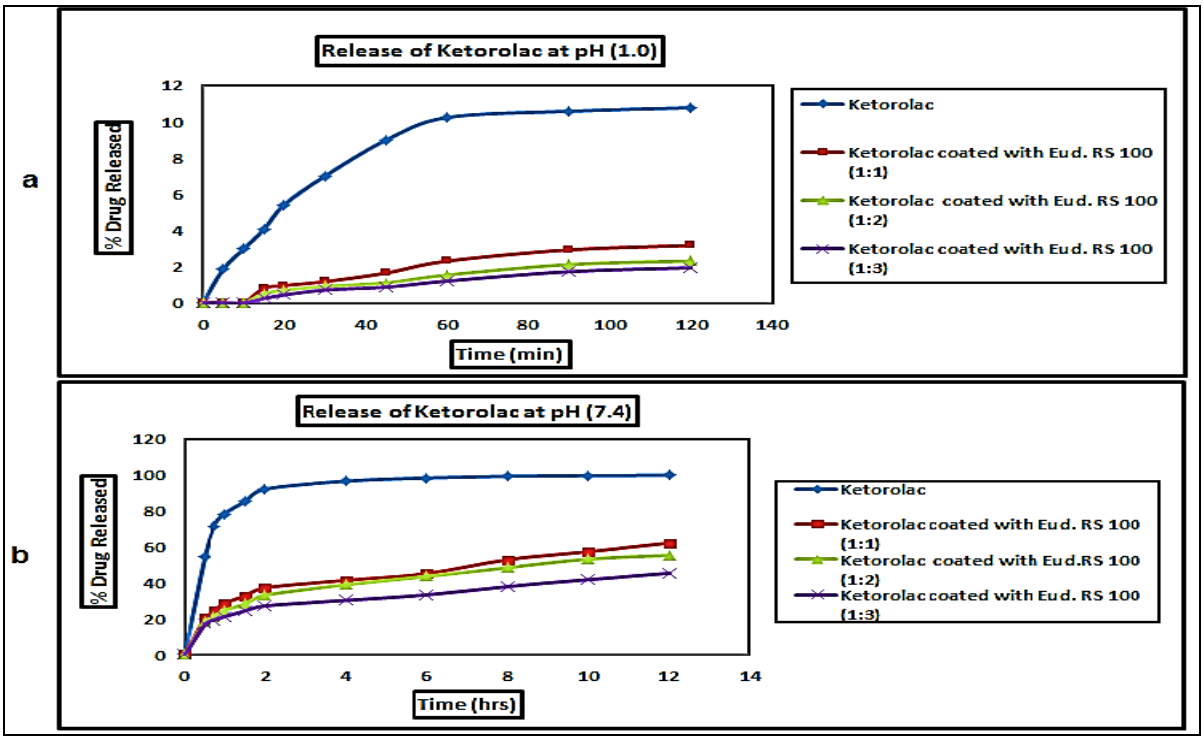

Figure (5): Release of ketorolac from its microcapsules with Eudragit RS 100, (a) in 0.1 N HCl (pH 1.0), (b) in phosphate buffer (pH 7.4).

Figure (5) shows a poor drug release ranging from 1.94±0.76% to 3.17±0.90% which was observed from the microcapsules 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.[36]

The drug release from the microcapsules in pH 7.4 depended on the total polymer levels. Microcapsules produced with Eudragit RS100 alone showed slow drug release ranging from 45.30±0.56% to72.12±0.17% 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 microcapsules.

At pH 1.0, the percentage released after 120 minutes of ketorolac in Eudragit RS100 microcapsules 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 released after 12 hours of ketorolac in Eudragit RS100 microcapsules at drug: polymer ratio of (1:1) showed 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 to decrease the percentage released of ketorolac 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 released after 120 minutes of ketorolac in Eudragit RS100 microcapsules 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 microcapsules in the ratio of (1:1).

At pH of 7.4, the percentage released after 12 hours of ketorolac in Eudragit RS100 microcapsules 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 microcapsules in the ratio of (1:1).

By increasing the ratio of the polymer to decrease the percentage released of ketorolac 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 RS100 microcapsules 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 microcapsules in the ratios of (1:1) & (1:2) respectively.

At pH of 7.4, the percentage released after 12 hours of ketorolac in Eudragit RS100 microcapsules 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 microcapsules in the ratios of (1:1) & (1:2) respectively at the same pH.

The slow drug release from microcapsules with Eudragit RS100 can be attributed to the low permeability of the polymer, which posed a significant hindrance to fluid penetration and passive drug diffusion.

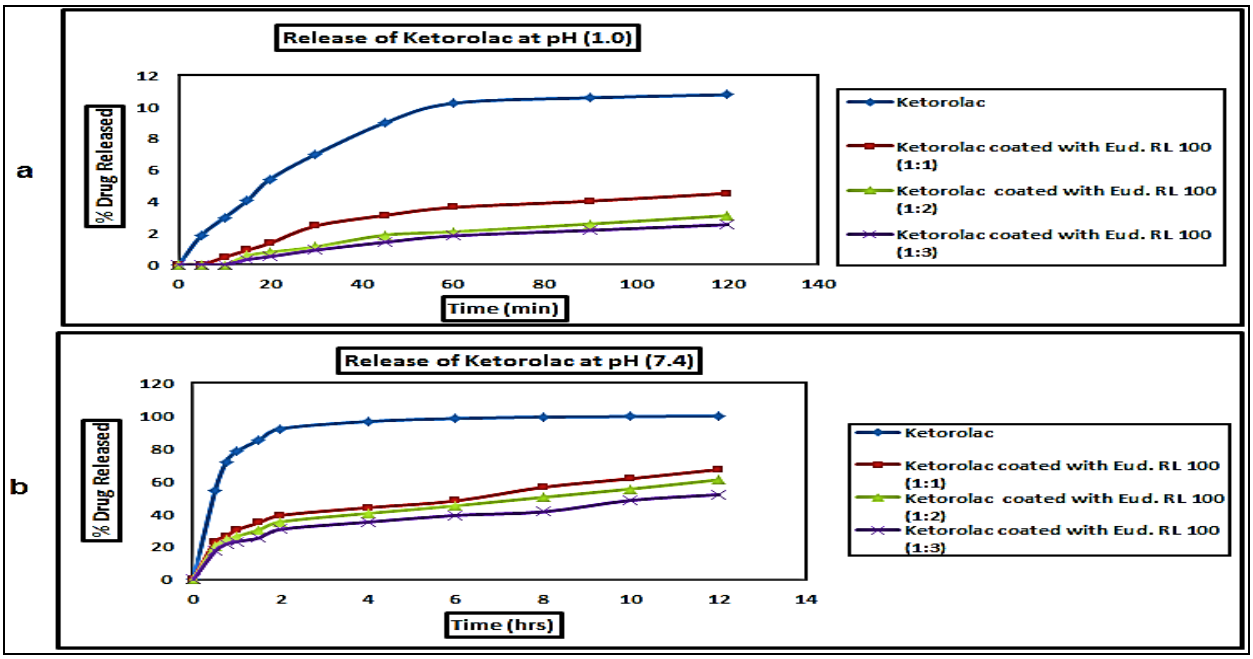

Figure (6): Release of ketorolac from its microcapsules with Eudragit RL 100, (a) in 0.1 N HCl (pH 1.0), (b) in phosphate buffer (pH 7.4)

Incorporation of the Eudragit RL100 is reported to enhance the drug release from the microcapsules.[37] The drug release from the microcapsules in pH 7.4 depended on the total polymer levels.

Figure (6) shows that microcapsules produced with Eudragit RL100 alone showed slow drug release ranging from 51.68±0.74% to67.13±0.39% 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 microcapsules.

At pH 1.0, the percentage released after 120 minutes of ketorolac in Eudragit RL100 microcapsules 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 released after 12 hours of ketorolac in Eudragit RL100 microcapsules at drug to polymer ratio of (1:1) showed 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 to decrease the percentage released of ketorolac 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 microcapsules 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 microcapsules (1:1).

At pH of 7.4, the percentage released after 12 hours of ketorolac in Eudragit RL100 microcapsules 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 microcapsules(1:1).

By increasing the ratio of the polymer to decrease the percentage released of ketorolac 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 microcapsules 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 RL100 microcapsules 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 microcapsules 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 microcapsules in the ratios of (1:1) & (1:2) respectively at the same pH.

This increase in percentage released compared with Eudragit RS100 was due to increased permeability and hydrophilicity of Eudragit RL00 because of the higher content of quaternary ammonium group in Eudragit RL00.

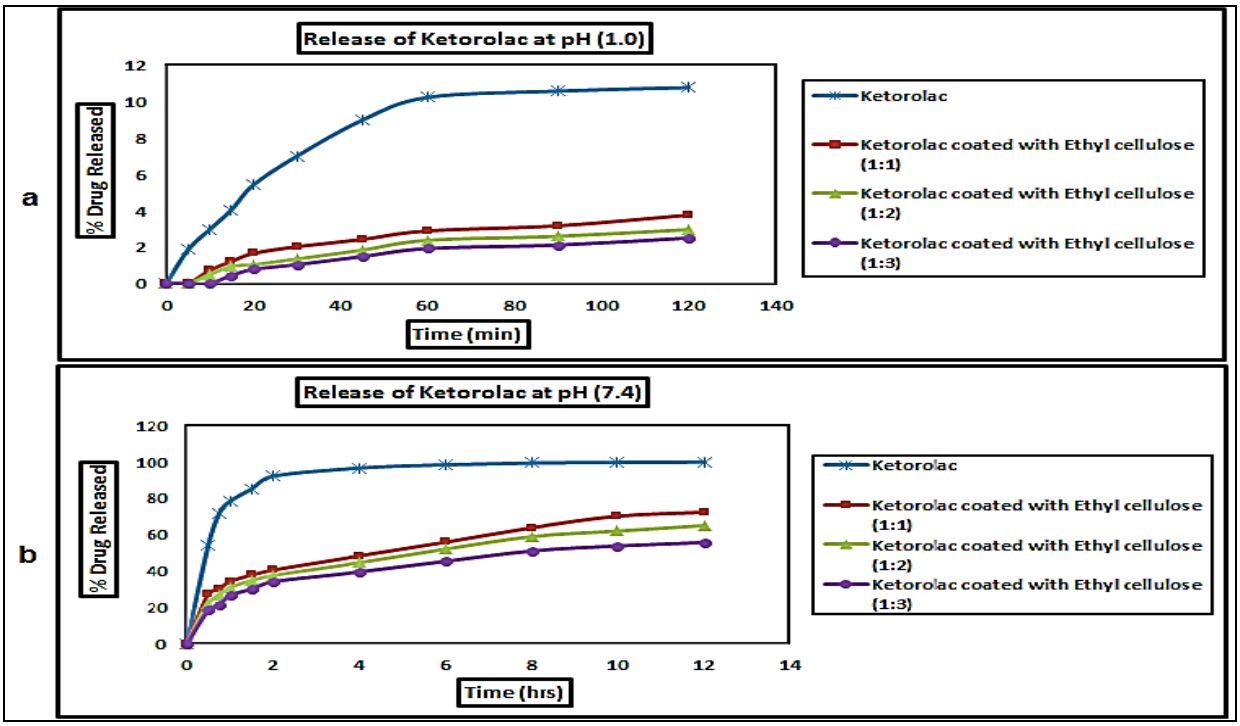

Figure (7): Release of ketorolac from its microcapsules with Ethyl cellulose, (a) in 0.1 N HCl (pH 1.0), (b) in phosphate buffer (pH 7.4)

The drug release from the microcapsules in pH 7.4 depended on the total polymer levels. Figure (7) shows that microcapsules produced with Ethyl cellulose alone showed slow drug release ranging from 55.61±0.23% to72.20±0.61% 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 microcapsules. This may be due to increase in system viscosity with the increase in Ethyl cellulose concentration.[38, 39]

At pH 1.0, the percentage released after 120 minutes of ketorolac in Ethyl cellulose microcapsules 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 Ethyl cellulose does not dissolve in acidic pH.

At pH of 7.4, the percentage released after 12 hours of ketorolac in Ethyl cellulose microcapsules 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 to decrease the percentage released of ketorolac 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 released after 120 minutes of ketorolac in Ethyl cellulose microcapsules 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 microcapsules in the ratio of (1:1).

At pH of 7.4, the percentage released after 12 hours of ketorolac in Ethyl cellulose microcapsules 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 microcapsules in the ratio of (1:1).

By increasing the ratio of the polymer to decrease the percentage released of ketorolac 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 Ethyl cellulose microcapsules 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 microcapsules (1:1) but not significant (p value > 0.5) than that of ketorolac in Ethyl cellulose microcapsules in the ratio of (1:2) at the same pH.

At pH of 7.4, the percentage released after 12 hours of ketorolac in Ethyl cellulose microcapsules 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 microcapsules 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 microcapsules 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 microcapsules 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).

3.8. Stability test

Table (3) 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, 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 all controlled release formulations.

Table (3): Stability of ketorolac in different prepared formulations.

Polymers used	Drug: polymer ratio	Time (Months)		
		1	3	6
Eudragit RS 100	1:1	99.22±0.98	98.34±1.34	97.17±1.23
	1:2	98.97±1.22	97.84±0.76	97.03±0.90
	1:3	99.08±0.65	98.87±1.46	97.87±1.76
Eudragit RL 100	1:1	98.78±0.87	97.54±0.88	96.43±0.65
	1:2	99.45±0.67	98.18±0.95	96.98±1.28
	1:3	98.79±0.43	97.39±0.89	96.45±1.49
Ethyl cellulose	1:1	99.81±0.90	98.56±0.75	97.32±0.46
	1:2	99.40±1.61	98.76±1.44	96.97±1.80
	1:3	97.98±0.98	96.67±0.45	95.97±1.08

From the table, the stability of ketorolac in these formulations was examined over six months. There was insignificant ketorolac degradation in the prepared e 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.

2.9. Kinetic analysis of the release of ketorolac

Table 4 and 5 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 (4): *In vitro* release characteristics of ketorolac from its microcapsules in 0.1 N HCL.

Formula	Drug: Polymer Ratio	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Release Mechanism	K (mg. $min^{-1/2}$)
Ketorolac-Eud.RS100	1:1	0.9208	0.9573	**0.9909**	Higuchi	1.32±0.324
	1:2	0.9313	0.9554	**0.9892**	Higuchi	4.21±0.364
	1:3	0.9255	0.9729	**0.9954**	Higuchi	1.32±0.114

Ketorolac-Eud.RL100	**1:1**	0.9407	0.9787	**0.9927**	Higuchi	1.92±0.147
	1:2	0.9499	0.9809	**0.9949**	Higuchi	3.44±0.065
	1:3	0.9474	0.9539	**0.9942**	Higuchi	5.61±0.038
Ketorolac-Ethyl Cellulose	**1:1**	0.9851	0.9778	**0.9955**	Higuch	8.19±0.191
	1:2	0.9811	0.9896	**0.9979**	Higuchi	2.43±0.064
	1:3	0.9678	0.9589	**0.9963**	Higuchi	7.32±0.431

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

Table (5): *In vitro* release characteristics of ketorolac from its microcapsules in phosphate buffer (pH 7.4).

Formula	Drug: Polymer Ratio	Zero Order (R^2)	First Order (R^2)	Higuchi (R^2)	Release Mechanism	K (mg. $min^{-1/2}$)
Ketorolac-Eud.RS100	**1:1**	0.9405	0.9623	**0.9964**	Higuchi	1.23±0.365
	1:2	0.9119	0.9537	**0.9857**	Higuchi	2.54±0.086
	1:3	0.9246	0.9749	**0.9886**	Higuchi	3.19±0.147
Ketorolac-Eud.RL100	**1:1**	0.9314	0.9534	**0.9931**	Higuchi	5.23±0.312
	1:2	0.9398	0.9484	**0.9947**	Higuchi	1.32±0.034
	1:3	0.9107	0.9634	**0.9962**	Higuchi	3.15±0.243
Ketorolac- Ethyl Cellulose	**1:1**	0.9003	0.9485	**0.9931**	Higuchi	4.41±0.097
	1:2	0.9166	0.9448	**0.9972**	Higuchi	2.38±0.130
	1:3	0.9469	0.9642	**0.9972**	Higuchi	1.87±0.359

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

From Tables (4& 5) 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

Air suspension technique has been successfully employed to produce ketorolac loaded microspheres with maximum drug encapsulation and desirable release profile. The formulation variable drug-polymer ratio exerted a significant influence on the drug encapsulation and drug release with improved bioavailability, efficient targeting and dose reduction. FT-IR studies did not reveal any 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. Therefore, one can assume that the ketorolac microcapsules are promising pharmaceutical dosage forms by providing controlled release drug delivery systems and avoiding the dose related side effects in the entire physiological region. The entire process is feasible in an industrial scale and demands pilot study.

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