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A NOVEL CHRONOTHERAPEUTIC SYSTEM OF ETORICOXIB FOR TIME SPECIFIC DELIVERY BY MICROSPHERES AND TABLET LOADED CAPSULE SYSTEM

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Abstract:
The aim of this study was to create an innovative delivery system for Etoricoxib (ET) that offers dual pulse release as a therapeutic approach for rheumatoid arthritis. This system involves the use of microspheres and a tablet-in-capsule arrangement (MT-C).The design of this system involves an impermeable hard gelatin capsule body, inside which a core tablet (the second pulse) is placed at the bottom and sealed with a hydrogel plug (HP). The capsule body is then locked with an enteric-coated cap filled with KT microspheres (the first pulse). The selection of microspheres for the first pulse involved screening different formulations, and ET-M1 was chosen due to its small particle size and high drug loading.The criteria for selecting the second pulse (CT-2) included a disintegration time of 94 seconds and a cumulative drug release (CDR) of 95.56±0.37%. The formulation that met these criteria and achieved the maximum CDR by the end of 6 hours was considered the best.The hydrogel plug (HP) tablet was chosen based on its ability to maintain a lag period of 6 hours. The optimized formulations were then assembled according to the proposed design to create the pulsatile MT-C system, which was evaluated for in vitro release.The MT-C system demonstrated a delayed sustained CDR of 96.25% by the end of 10 hours from the first pulse (microspheres) after a 2-hour lag time. This was followed by a rapid release of ET from the second pulse (core tablet) in simulated colonic fluid within 10 hours.In conclusion, the in vitro pulsatile release system achieved a rational combination of delayed sustained and immediate release of ET. This system has the potential to address pain during the night and morning stiffness associated with rheumatoid arthritis. Incorporating two pulses into one system offers the advantage of reducing the frequency of dosing and improving pain management.

Keywords:- Etoricoxib, Chronotherapeutic system, Microspheres, Rheumatoid arthritis

Introduction:

Rheumatoid arthritis (RA) is an autoimmune disease that causes long-term joint inflammation and can lead to major disability and death at a young age. RA causes joint membrane inflammation that lasts for a long time. As the disease gets worse, this causes periarticular bone erosion, damage to the articular cartilage, permanent abnormalities, and signs of the disease outside of the joints [1,2]. Getting older is one of the most important things that can cause RA [3]. RA is thought to affect

about 1% of the world's population, and women are two to three times more likely to get it than men [4]. The rate of RA in India is between 0.28 and 0.7%, which is close to the rate in rich countries [5]. People of all ages can get RA, but it happens most often in people between the ages of 30 and 50 [6]. RA can affect any joint in the body. But it mostly affects the wrists and knees, especially the proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints [7]. People with RA feel most of their pain in their hands. Also, there have been some changes in how often pain and swelling happen. Large joints like the elbow, shoulder, and knee tend to hurt, and small joints like the metacarpophalangeal joints tend to swell [8].
Chronotherapeutic drug delivery systems are becoming more important in the field of pharmaceutical technology because they cut down on the number of doses, lower toxicity, and give the drug that fits the CR of the disease when the symptoms are at their worst. Chrono pharmaco therapy has been allowed for rheumatoid arthritis to make sure that the most of the drug is in the blood when the pain and stiffness are the worst[9]. It has been shown that people with rheumatoid arthritis have different amounts of C-reactive protein and interleukin-6 in their blood every 24 hours. Opioid peptides are made by the body. They are at their highest in the morning and at their lowest in the evening. This is true for both kids and adults[10]. People with rheumatoid arthritis feel the most pain in the morning because of the chemicals in their bodies. The pain goes away as the day goes on. Since this is the case, the best way to treat rheumatoid arthritis is with chronotherapy.
In rheumatoid arthritis (RA), nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used either in combination with disease-modifying antirheumatic drugs like methotrexate or as standalone therapy to alleviate symptoms [11]. Although NSAIDs effectively manage joint pain and swelling in RA, their side effects can limit their use in some patients. Traditional nonselective NSAIDs, in particular, are associated with significant gastrointestinal toxicity, which can be a major drawback [12]. Gastrointestinal complications such as bleeding, ulceration, and perforation are the most common and serious adverse events linked to NSAIDs. These issues often force patients to discontinue NSAID treatment and necessitate costly treatment for gastrointestinal symptoms [13]. RA patients, especially those exposed to high doses of NSAIDs over an extended period and those concurrently using steroids, are at a heightened risk of experiencing gastrointestinal-related adverse events [14,15].

The emergence of a new generation of NSAID treatments that selectively target cyclooxygenase-2 (COX-2) while sparing COX-1 provides an alternative therapeutic option for many RA patients and individuals with other inflammatory disorders [16]. Previous studies have demonstrated the effectiveness and favorable tolerability of selective COX-2 inhibitors like rofecoxib and celecoxib as treatments for RA. These drugs have shown a reduced risk of gastrointestinal toxicity compared to nonselective NSAIDs [17,18]. A recent clinical trial conducted in the United States investigated the use of the highly selective COX-2 inhibitor etoricoxib (at a dose of 90 mg) for the treatment of RA. The trial not only confirmed the effectiveness of etoricoxib but also suggested that this particular dose of etoricoxib may be more effective than a 1000-mg dose of the non-selective NSAID naproxen [19]. This present study, conducted at various sites around the world, further examines the clinical profile of etoricoxib 90 mg in RA patients.

With microsphere-based therapy, different combinations of drugs and polymers can be used to control how drugs are released at each treatment spot. With the help of microspheres, bioactive agents might be able to last longer and their release into the body could be controlled. Even though microspheres are small, they have a high ratio of surface area to volume.

The aim of this study was to develop an innovative pulsatile-release drug delivery device designed to administer medication at a precise time and location. In summary, the system comprises sustained-release microspheres (constituting the first pulse) enclosed within an enteric-coated capsule cap, which securely seals the impermeable capsule body (also coated with enteric coating).

Within this capsule body, there is a swellable hydrogel plug (HP) positioned at the opening, below which an immediate-release core tablet is housed to provide the second pulse (immediate release). The selection of both the first and second pulses, as well as the hydrogel plug (HP2), was made following a thorough evaluation of their respective formulations. The MT-C (Microsphere and tablet in capsule system) system's in vitro release would be tested to confirm the biphasic release behaviour.

MATERIALS AND METHODS

Materials

Etoricoxib was generously provided as a gift sample by Dr. Reddy's Laboratories located in Ahmadabad, India. Ethyl cellulose was sourced from Yarrow Chemicals in India, while Eudragit RS100 was obtained from Sigma Aldrich. Microcrystalline cellulose, magnesium stearate, methanol, and dichloromethane were procured from S.D. Fine Chemicals based in Mumbai, India. All other necessary chemicals were acquired from local suppliers.

Design of microspheres and tablet in capsule system

In order to make MT-C, the hard gelatin pill shell had to go through two different steps that gave it two different roles. Enteric was used to cover the outside of the capsule cap, and ethylcellulose was used to cover the inside of the capsule body to make it waterproof. To make MT-C, the core tablet of the second pulse and the HP tablet were put in the airtight body and covered with an enteric-coated cap that had microspheres in it. Figure 1 shows the process step by step [20].

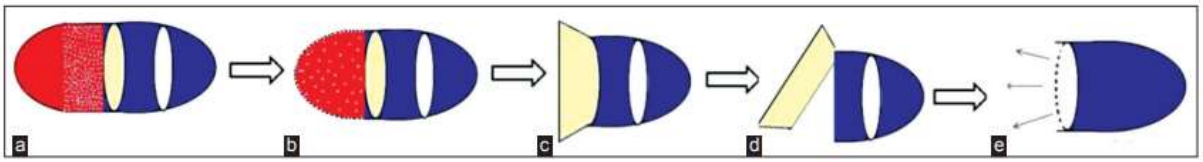


Figure 1: Schematic representation of the proposed release of drug in dual pulse from microspheres and tablet in capsule system. (a) Lag time (t = 2 h) with no drug release, (b) sustain drug release from first pulse (microspheres, t = 8 h), (c) swelling of plug tablet in simulated intestinal fluid no drug release, (d) ejection of plug tablet in colonic fluid (e) immediate drug release from second pulse (t = 10 h)

Bifunctional capsule shell (impermeable capsule body with enteric cap)

STEP-1:

Coating of capsule cap

As a solvent, acetone:ethanol (8:2 v/v) was used, and dibutyl phthalate (0.75 v/v) was added as plasticizer. This made a 5% by weight/volume solution of cellulose acetate phthalate. Dip coating was used for enteric coating of capsule cap." The caps were put in a solution of cellulose acetate phthalate and dried for 24 hours at 37°C +0.5°C. Coating was done over and over again until the cap didn't break down in 0.1N HCl buffer, pH1.2 for at least 2 hours. Japan's mitoyuto vernier calliper was used to measure the coated capsule shell [21].

Impermeable capsule body

The following text describes the creation of impermeable gelatin capsule bodies using ethyl cellulose as a coating material, with varying concentrations of ethyl cellulose. The aim was to produce capsules with different coating strengths. A mixture of ethyl acetate, dichloromethane, and ethanol in a 4:0.8:0.2 ratio was prepared, to which ethyl cellulose was added, resulting in solutions with concentrations of 40 g/l, 80 g/l, and 120 g/l of ethyl cellulose.

Next, 0.55 ml of each ethyl cellulose solution was poured into uncapped gelatin capsule bodies (size 0). These capsules were left in a refrigerator at 4°C overnight to allow the solvent to evaporate. The impermeable capsule bodies were then stored in a desiccator for future use. The thickness of the internally coated capsule shell was measured using a screw gauge and recorded in millimeters (n = 3). Additionally, the lock length of the capsule was measured using a vernier caliper.

STEP-2:

Etoricoxib loaded microspheres (first pulse)

The ET-filled microspheres were made using the liquid evaporation method[10]. To make a solvent, 8 ml of a blend of 5:3 parts methanol to 3 parts acetone was mixed with Eudragit RS100. Then 100 mg of ETand 50 mg of magnesium stearate were added. The dispersion was mixed with 60 ml of light paraffin oil, 6.8 ml of n-hexane, and 1500 rpm of mixing by mechanical strirrer [22]. To make the microspheres, the liquids (acetone and methanol) were added until they were disappeared. 50 ml of hot petroleum ether was used to filter and clean microspheres that had already been made. At room temperature, ET-filled microspheres were dried for 24 hours. The microspheres were then put in a dry box with melted calcium chloride until they were needed again. Six different formulations were made by changing the amount of eudragit RS100 but keeping the amounts of the drug, magnesium stearate, and organic solvents the same [Table 1].

Table 1. Formulation of ET loaded Microspheres.

S. No	Formulation	Drug : Polymer (by weight)
1.	ET-M1	1:1
2.	ET-M2	1:2
3.	ET-M3	1:3
4.	ET-M4	1:4
5.	ET-M5	1:5
6.	ET-M6	1:6

Particle size and percentage yield

The size of the microspheres' particles was measured with an optical lens. The sample was put on a clean slide, and an eye piece micrometre was used to look at it through a microscope. Size tests were done on about 300 microspheres, and the average size was found[23]. By dividing the weight of the finished microspheres by the overall amount of drug and excipients used, the percent yield of ET-loaded microspheres was found.

Entrapment efficiency and drug loading

Microspheres filled with ketorolac tromethamine were broken up with a glass mill and mortar, and 10 mg of the drug was taken out with 5 ml of a 7.4 pH phosphate buffer. This took 30 minutes. After the solution was well mixed, 0.45 m membrane filter paper was used to separate it. 10 millilitres were made from 1 millilitre of the mix. An ultraviolet spectrophotometer (Shimadzu Pharmaspec1700, Kyoto, Japan) was then used to look at the solution at 233 nm. To figure out how well the traps work and how much drugs they carry, the following models were used:

$$\text{Percent entrapment efficiency} = \frac{\text{Practically entrapped amount of drug}}{\text{Total amount of drug}} \times 100$$

$$\text{Percent loading efficiency} = \frac{\text{Drug loaded in microspheres}}{\text{Total weight of microspheres}} \times 100$$

In vitro drug release

10 mg of ET equivalent microspheres were put into a USP I basket, and the study was done in 900 ml of phosphate buffer, pH7.4, at 50 rpm and 37°C±0.5°C for 6 hours. At regular intervals for 6 h, 5 ml aliquots were taken out, and the same amount of fresh release medium was added to keep the sink conditions the same. Samples were looked at with spectrophotometry at lamda max of 233 nm, and plots of % CDR vs. time were made.

Selection of optimized formulation

Optimized formulation has been selected for further on basis of smallest particle size, highest trapping efficiency, and highest CDR.

Scanning electron microscopy

The JEOL-6360A, an analytical scanning electron microscope (JEOL 6360A, Tokyo, Japan), was used to look at the better TS microspheres (M1). A machine called an ion spark was used to put gold into the dry sample. Using an increasing voltage of 20 KV, different levels of magnification were used to look at the microspheres, and pictures were made by randomly scanning the counterfoil.

Micromeritic properties

Micromeritic evaluation of the microspheres was conducted to assess their flow properties, packing properties, and porosity, with the aim of determining their suitability for use in tablet formation or capsule filling. To achieve this, a measured amount of microspheres was transferred into a graduated cylinder from each batch to determine both the bulk and tapped density. This was carried out using a USP-I tapped density tester (TD 1025, Lab India Instruments, Mumbai, India). The angle of repose (h) was determined using the fixed funnel method. Bulk characterization parameters were chosen to assess the flow properties.

STEP-3: Formulation of 2nd pulse core tablet

Core tablets of ETwere made by using Karnavathi 9 station punching machine as per the formula mentioned din Table 2. The ingredients were put through a #60 mesh sieve and mixed in the right amounts for 15 minutes in a polybag. After that, magnesium stearate and talc were added, and 100 mg pills were made. Each ETfast disintegrating tablet contained 10 mg of dose.

Table 2. Formulation of core tablets for 2nd pulse

Formulations Code	Super disintegrating agent	Mannitol	Starch	Talc & Magnesium stearate
CT-1	SSG-2 mg	Q.S to make 100 mg tablet	8 mg	2 mg
CT-2	SSG-4 mg	Q.S to make 100 mg tablet	8 mg	2 mg
CT-3	SSG-6 mg	Q.S to make 100 mg tablet	8 mg	2 mg
CT-4	CP- 2 mg	Q.S to make 100 mg tablet	8 mg	2 mg
CT-5	CP- 4 mg	Q.S to make 100 mg tablet	8 mg	2 mg
CT-6	CP- 6 mg	Q.S to make 100 mg tablet	8 mg	2 mg

(SSG- Sodium Starch Glycolate; CCS- Crospovidone)

Evaluation of core tablet

The core tablets underwent a series of tests, including selected pharmacopoeial (uniformity of weight, uniformity of content) and nonpharmacopoeial tests (thickness, hardness, friability). Here is a breakdown of these tests:

1. **Uniformity of Weight:** This test assessed the consistency of tablet weight among a sample of 20 tablets. The methodology followed the guidelines outlined in IP 2007.
2. **Uniformity of Content:** This test aimed to ensure that the drug content was uniform across the core tablets. Specific pharmacopoeial standards were followed for this assessment.
3. **Hardness and Thickness:** To determine tablet hardness (n = 6), a Monsanto hardness tester was employed. For measuring tablet thickness (n = 6), a Vernier caliper was used.
4. **Friability:** The friability of the tablets (n = 6) was assessed using a Roche friabilator. The method used for this test was described in <1216> general information, USP 27/NF 22.
5. **Drug Content:** To determine the amount of drug present in the tablets, 10 tablets were crushed, and 100 mg of the resulting powder was extracted with 10 ml of methanol. The mixture was then filtered through Whatman filter no.1, and the drug content was assessed at a wavelength of 233 nm. This measurement was made using a validated calibration curve.

In vitro release

For the in vitro release study, 900 ml of phosphate buffer with a pH of 6.8 was used as the dissolved liquid in a USP II dissolution device. The medium was kept at a temperature of 37°C + 0.5°C and stirred at 100 rpm. At 0 minutes, 5 minutes, 10 minutes, 15 minutes, 20 minutes, and 30 minutes, 5 ml of the sample was taken out and replaced with the same amount of new medium. At max = 233 nm, spectrophotometry was used to look at the samples.

STEP-4:

Hydrogel plug tablet formulation and evaluation

Using a 6 mm single punch machine, equal amounts of HPMC K4M and lactose (50 mg and 50 mg) were pressed together to make a hydrogel plug pill that would seal the capsule body. A vernier calliper and a Pfizer hardness test machine (HICON® Grover Enterprises, New Delhi, India) were used to measure the thickness and hardness of the core tablets. From each batch, five tablet were chosen at random and their hardness was tested in kilogrammes per square centimetre.

Swelling index

In the right order, three different pH solutions were added to each batch of hydrogel plug pills. A plug tablet (W1) and 200 mL of pH 7.4 phosphate buffer were put into a glass jar and left there for 6 hours. At 6 hours, the plug tablets were taken out, and a filter paper was used to carefully remove the fluids on top. A second time, the pill was weighed (W2). The following method was used to figure out the swelling score. (SI):

$$SI = \frac{\text{Wet weight (W2)} - \text{Dry weight (W1)}}{\text{Wet weight (W2)}} \times 100$$

Lag time

Indirectly, lag time was found by timing how long it took for HP2 to be thrown out. This was done because the drug from the core pill (second pulse) wouldn't be released until the swollen HP2 got all the way out of the mouth of the solid capsule body. For the study, an airtight capsule body with a core tablet in the bottom and an HPMC K4M HP2 tablet in the mouth was connected to the paddle of the USP apparatus II and suspended in phosphate buffer, pH 7.4, for 8 hours. The lag time was measured by how long it took for the plug tablet to come out of the mouth of the solid capsule body. Also, the drug release from the core pill was checked every 30 minutes for a total of 8 hours.

Step 5:

Assembly of microspheres and tablet in capsule system

The optimized formulation of microspheres and the core tablet were filled into capsule shell to get two different pulse releases at different sites. To do the same thing, the optimized core tablet containing 10 mg of ET was put in the bottom of the airtight body, and an HP tablet was used to stop the mouth of the body. The MT-C was made by putting 10 mg of ET into microspheres and then putting them in a pill cap with an enteric coating. The body of the package was then sealed with a cap. The setup was put out in the lab [25]**.**

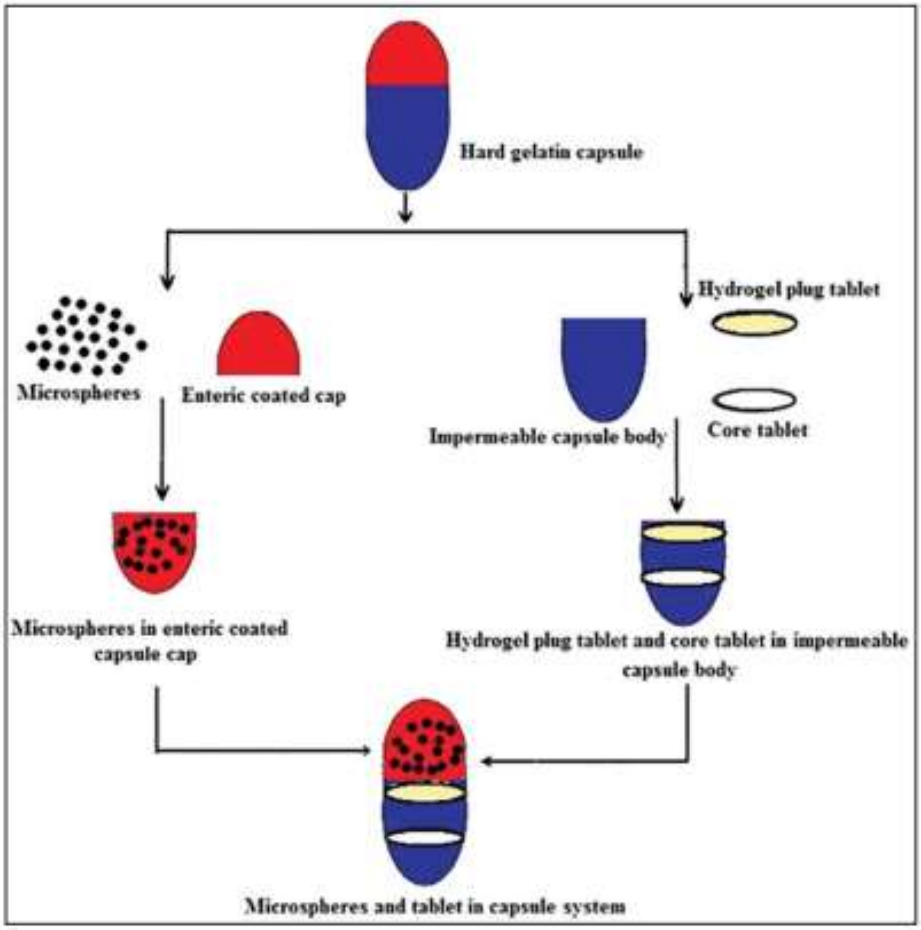


Figure 2: Step by step Formulation approach of microspheres and tablet in capsule system [26].

In vitro release

As the preparation was designed to traverse through the entire gas troint estinal tract to safely reach colon after oral administration, three dissolution media were sequentially used. Using USP tools II and a 100 rpm stirrer, the MT-C device was put through an in vitro drug release test. Sinkers were used so that the capsules would be fully submerged in the dissolution medium and not float to the top. First, drug release was tested in a 900 ml hydrochloric acid buffer with a pH of 1.2 and a temperature of 37°C 1°C for 2 hours. Every hour, a small amount of the breakdown fluid was taken, filtered through Whatman filter paper no. 1, and tested for the amount of ET at 233 nm. After 2 hours, the solution was changed to a 7.4 pH phosphate buffer. Every hour for the next six hours, samples of 5 ml were taken and measured at 233 nm. After 8 hours, the medium was taken away and replaced with phosphate buffer, pH 6.8, so that the release studies could continue for another 2 hours. For each sample that was taken out, a new medium for dissolving was put in its place. The charts were made and looked at to see how percent CDR changed over time.

Stability studies:
Short-term stability studies were conducted for the MT-C system following ICH guidelines. Capsules were sealed in amber glass bottles with rubber corks and placed in stability chambers. These chambers maintained conditions at 40°C ± 2°C with 75% RH ± 5% RH and 25°C ± 2°C with 60% RH ± 5% RH for about two months. Samples were collected at intervals and analyzed for physical appearance, drug content, and in vitro drug release [27].

RESULTS AND DISCUSSION

Bifunctional capsule

The primary goal of the bifunctional capsule was to achieve targeted pulsatile drug delivery at a specific site. To accomplish this, the capsule structure was designed with distinct features: the cap was coated with an enteric layer, and the body was coated with ethyl cellulose to ensure one-way drug release in the colon. The enteric coating was applied externally to the capsule shell, while the ethyl cellulose coating was applied internally. The coating process was carefully optimized using a dip-coating method. The thickness of the enteric-coated cap ranged from 0.006 mm to 0.054 mm, with an increase in thickness observed with multiple coating layers. Consequently, the cap with triple coating had a thickness of 0.054 ± 0.41 mm.

In contrast, the thickness of the ethyl cellulose-coated impermeable capsule body varied between 0.017 mm and 0.068 mm, depending on the concentration of ethyl cellulose used. Higher concentrations of ethyl cellulose resulted in a thicker impermeable capsule body. Controlling the thickness of the impermeable capsule body was critical to ensure mechanical strength and prevent premature drug release from the body. Among the tested compositions, IC3 (12% ethyl cellulose) was identified as the most impermeable capsule body, a characteristic further confirmed by subsequent in vitro release studies.

The optimized enteric-coated capsule cap and impermeable capsule body were then assembled and assessed for their lock length, which measured at 22.9 ± 0.16 mm.

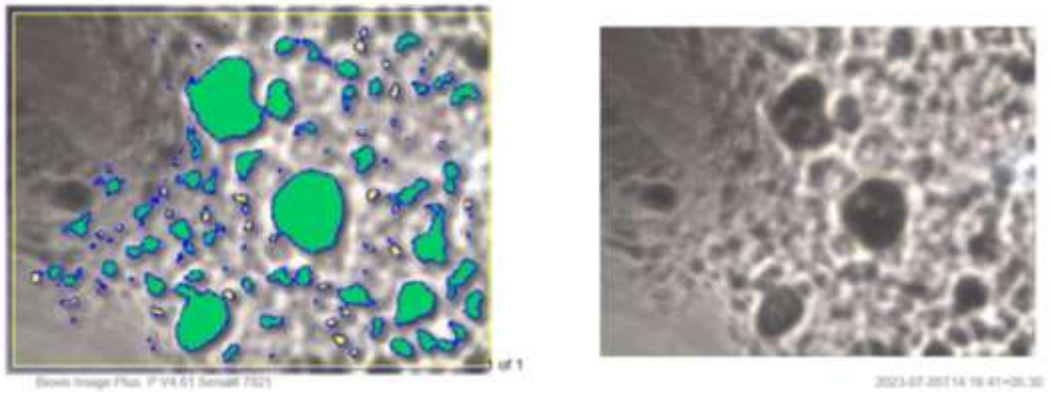
EBloaded microspheres

The particle size of the microspheres loaded with EB ranged from 19.87±0.07 to 223.47±0.34 μm [Figure 3]. As the polymer concentration increased, there was a noticeable increase in the average microsphere size. This was primarily due to the heightened viscosity, resulting in larger droplet sizes during microsphere formation. Consequently, there was a corresponding increase in both the percent yield and entrapment efficiency of the microspheres as the drug-to-polymer ratio increased [Table 2]. M6 exhibited the highest percent yield and entrapment efficiency because the elevated polymer concentration led to the formation of larger microspheres, thus increasing the overall product yield.

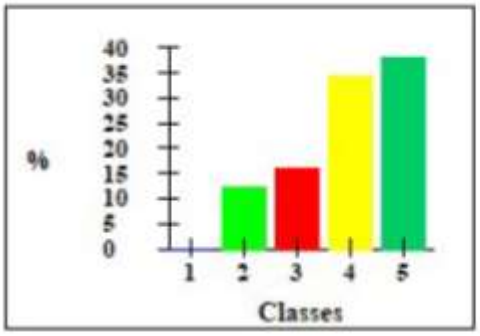
In contrast, the drug loading efficiency of the microspheres loaded with ET ranged from 37.25±0.58 to 25.09±0.68% [Table 3]. Similar to the EB-loaded microspheres, an increase in polymer concentration resulted in larger microsphere sizes due to increased viscosity during formation. This, in turn, led to higher percent yield and entrapment efficiency with an increasing drug-to-polymer ratio. ET-M1 demonstrated the highest percent yield, entrapment efficiency, and drug loading efficiency for the same reasons mentioned earlier, where increased polymer concentration facilitated the formation of larger microspheres and improved overall product yield.Furthermore, these microspheres exhibited favorable flow properties, as evidenced by the angle of repose, Hausner's ratio, and Carr's index.

Table 3. Characterization of ET microspheres

S. No	Formulation	Yield (%)	Particle size (µm)	Entrapment efficiency (%)	Drug Loading (%)	CDR (%) 6 h
1.	ET-M1	88.25	19.87±0.07	81.87±0.45	37.25±0.58	88.92
2.	ET-M2	72.25	21.12±0.12	76.21±0.32	31.64±0.47	65.86
3.	ET-M3	65.78	44.65±0.19	79.47±0.51	29.86±0.32	72.35
4.	ET-M4	58.61	115.59±0.36	81.25±0.62	28.45±0.29	58.68
5.	ET-M5	69.21	189.72±0.41	83.26±0.49	26.12±0.21	56.25
6.	ET-M6	71.89	223.47 ± 0.34	85.19±0.56	25.09±0.68	51.21



(a)



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(b)

Figure 3. a) Microscopic images, b) Particle size and size distribution of ET loaded microspheres

The in vitro release profile of ET-loaded microspheres displayed a biphasic pattern [Figure 4], characterized by an initial burst release during the first hour due to drug located on the surface of the microspheres. This was followed by a sustained release phase extending up to 6 hours, attributed to the drug entrapped within the matrix of the microspheres. Notably, formulation ET-M1 exhibited the highest Cumulative Drug Release (CDR) of 88.92%, while ET-M6 displayed the lowest CDR at 51.21%. This observation clearly underscores the significant influence of Eudragit RS100 concentration on the extent of drug release. An increase in Eudragit RS100 concentration led to larger particle sizes, consequently resulting in an increased diffusional path length and a subsequent reduction in drug release rate.

To gain insights into the mechanism governing drug release, the release data was fitted to various release models. The Higuchi model provided the best fit, with the highest coefficient of determination (r^2 = 0.9995) observed for ET-M1. When the data was subjected to the Korsemeyer-

Peppas model, the value of 'n' was found to be <0.5, indicating that Fickian diffusion governed the drug release mechanism. Therefore, considering particle size, entrapment efficiency, and CDR, ET-M1 was identified as the optimized formulation.

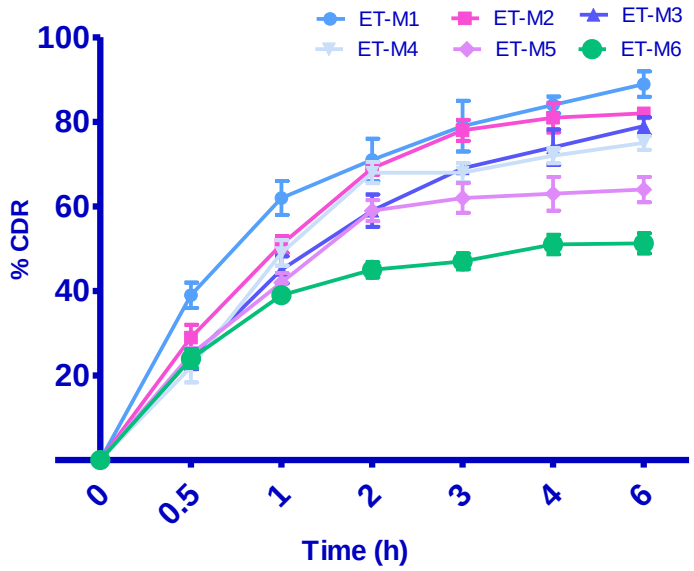


Figure 4. In vitro drug release profile of ET loaded microspheres.

To examine the external morphology and shape of ET-M1, scanning electron microscopy (SEM) analysis was conducted. The SEM micrograph [Figure 5] revealed spherical particles with diameters ranging between 100 and 500 µm. Upon closer inspection of the microspheres' outer surface, magnification revealed the presence of tiny pores. These pores were a result of the evaporation of the organic solvents (acetone and methanol) trapped within the microsphere shell during production. The overall surface appeared remarkably smooth and devoid of any notable imperfections.

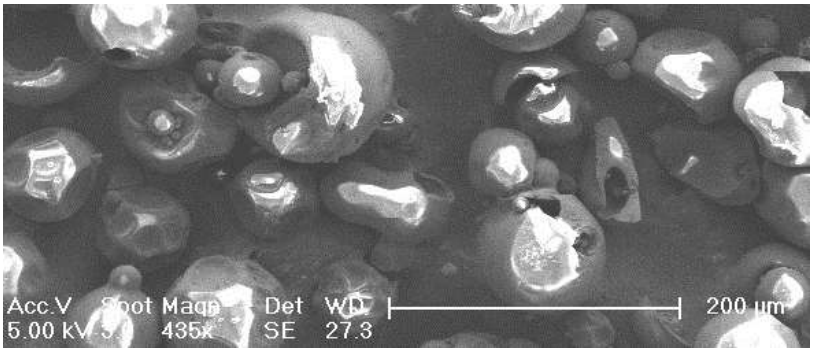


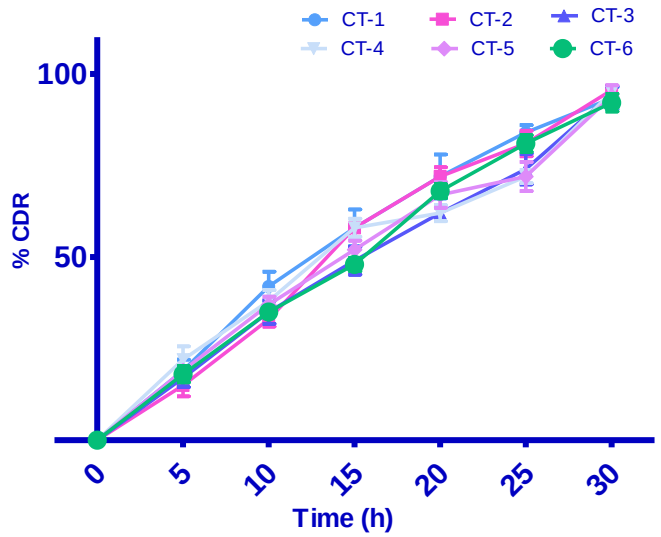
Figure 5. SEM image of micropsheres.

Core tablet of KT

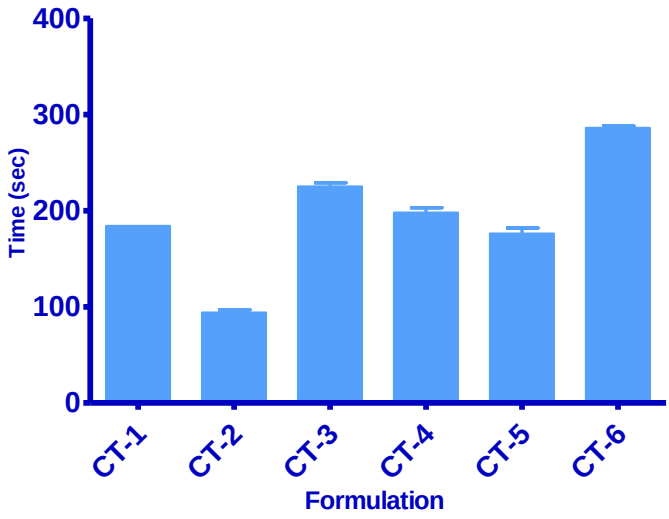
Several non-pharmacopeial and pharmacopoeia characteristics of the tablets were evaluated, indicating favorable physical attributes. The tablet thickness fell within a narrow range, from 4.03±0.05 to 4.15±0.07 mm, with low standard deviation values, signifying uniformity in thickness. Tablet hardness, reflecting their crushing strength, ranged between 3 and 4 kg/cm². The friability of the tablets was found to be within the official limit (<1), ensuring their structural integrity. The tablets exhibited weight variation within a range of 2%, adhering to acceptable standards. Furthermore, the tablets maintained drug content within pharmacopoeial limits. Regarding in vitro drug release, the tablets consistently achieved 93.35±0.25% to 95.56±0.37% Cumulative Drug

Release (CDR) within the first 30 minutes [Figure 5-a]. Notably, there was no significant difference observed in the extent of drug release among the tablets. However, the influence of the super disintegrant was evident in the form of an initial burst release within the first hour.

Given that the in vitro dissolution test did not provide sufficient differentiation among the tablets, the selection criteria relied on in vitro disintegration time. Consequently, tablet CT-2, which exhibited the shortest disintegration time of 94 seconds [Figure 5-b], was chosen for the fabrication of MT-C.



(a)



(b)

Figure 5. a) Disintegration and b) Dissolution profile of core tablets.

Hydrogel plug tablet

The formation of HP tablets was achieved through direct compression, and it was observed that the thickness of these plug tablets increased in direct proportion to the weight of the tablet, with the tablet diameter being kept constant at 6.78±0.45 mm, thanks to uniform tablet tooling. Interestingly, variations in weight had a negligible impact on the hardness of the plug tablets, which consistently fell within a narrow range of 7-8 kg/cm².However, relying solely on physical characteristics was insufficient for identifying the most suitable plug material. Therefore, the plug tablets underwent swelling studies. The swelling indices (SI) of HP were found to be 68.92±2.45%. Notably, as the

tablet weight increased, so did the SI, a logical outcome given that higher amounts of gelling polymer inherently possess greater fluid-absorbing capacity. Over the course of the study, a gradual increase in the swelling indices was observed with an increasing quantity of HPMC K4M and lactose. This phenomenon can be attributed to HPMC's ability to absorb water due to the presence of hydrophilic groups within its structure. The hydration of these functional groups facilitated the entry of water into the polymer network, leading to the expansion of the plug.
In addition to swelling characteristics, the lag time was also assessed to optimize the HP tablet. As described in the methodology section, an assembly comprising the impermeable capsule body housing a core tablet at the base and an HPMC K4M HP tablet snugly positioned at the mouth of the capsule body was utilized to determine the lag time by monitoring drug release. The results indicated that the lag time for drug release increased with the escalating weight of the plug tablet. Consequently, HP exhibited the longest lag time of 8 hours. These lag time studies also underscored the effectiveness of the plug tablet in maintaining unidirectional drug release, a feat made possible by the impermeable nature of the capsule body, which was internally coated with EC.

Microspheres and tablet in capsule system of EB

The formulation involving microspheres and a tablet-in-capsule system exhibited no release in the hydrochloric acid buffer with a pH of 1.2. This lack of release was due to the combined effects of the impermeable capsule body and the enteric-coated capsule cap. The pH-dependent enteric coating on the capsule cap remained un-ionized in this acidic medium, effectively preventing drug release. However, the scenario changed when the capsule was exposed to a phosphate buffer with a pH of 7.8. The pH-dependent polymer coating, cellulose acetate phthalate, dissolved in this medium, initiating the release of the first pulse (microspheres) [Figure 6]. Simultaneously, the hydrogel plug (HP) came into contact with the release medium and began to swell. The analysis of drug release from the first pulse (microspheres) exhibited a biphasic pattern, with 15.84% Cumulative Drug Release (CDR) occurring in the 3rd hour, followed by a substantial 82.17% CDR by the end of 8 hours. The sustained drug release was attributed to the property of Eudragit RS100, which formed a dense matrix structure.

Concurrently, the HP tablet absorbed the surrounding media and swelled into a frustroconical shape. In this form, it gradually pushed itself out of the capsule body. After a lag time of 7 hours, the HP2 tablet was ejected from the capsule body's mouth. Subsequently, the second pulse came into contact with a phosphate buffer with a pH of 6.8, initiating the release of the drug from the core tablet. The second pulse displayed a CDR of 96.25% by the end of 10 hours. This release profile can be attributed to the high swelling capacity and water uptake ability of croscarmellose sodium, which facilitated rapid disintegration. Additionally, the wetting properties of microcrystalline cellulose allowed for the absorption of a significant amount of fluid, hastening the dissolution rate and promoting the fast release of the drug from the core tablet within the MT-C system. In summary, this designed drug delivery system is well-suited for the treatment of rheumatoid arthritis due to its advantages such as reduced dose frequency, avoidance of dose dumping, and improved patient compliance, as it eliminates the need for early morning drug administration while ensuring targeted and time-specific delivery.

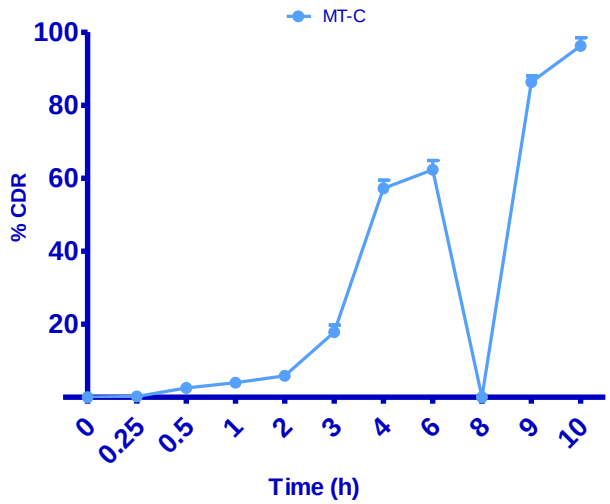


Figure 6. Drug release profile of MT-C system.

Stability studies:
Short term stability studies were performed for MT-C with the help of ICH guidelines. All the capsules maintained at 40 ◦C ± 2 ◦C+75% RH ± 5% RH and 25 ◦C ± 2 ◦C+60% RH ± 5% RH for about 2 months shown non-significant change in physical appearance, drug content, and in vitro drug release.

Conclusion
The MT-C system for delivering Etoricoxib, designed to address the late-night pain and morning stiffness associated with rheumatoid arthritis, has been successfully developed. The optimized formulation effectively achieved sustained and complete release of Etoricoxib through the microspheres, with a controlled lag time of 2 hours, thereby avoiding gastric delivery. The inclusion of the HP tablet, inserted into the mouth of the impermeable capsule body, served to shield the core tablet from the harsh environment of the stomach (SIF). After a predetermined lag time of 6 hours, the plug tablet was ejected, enabling the release of the intact core tablet in the simulated colonic fluid (SCF). This innovative design offers the potential to eliminate the need for a two-time daily administration regimen. In conclusion, the MT-C system demonstrated its versatility with variable multipulse release, comprising slow and fast pulses, tailored to meet the chronotherapeutic requirements of patients with rheumatoid arthritis.

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Conflicts of interest:
None

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