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ETODOLAC DOSAGE FORMULATION AND PROCESS FOR PREPARING THE SAME

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Abstract--- *Etodolac belongs to the class of "non-steroidal anti-inflammatory class of drugs" (NSAIDs) with anti-inflammatory, analgesic and anti-pyretic effects. At lower doses, NSAIDs provide analgesic properties, while higher doses are needed to produce anti-inflammatory action. The treatment of osteoarthritis, rheumatoid arthritis and relatively extreme post-surgical pain relief is effective with Etodolac. Etodolac was used in the treatment of ankylosing spondylitis, post-operative pain (dental, orthopedic or obstetric surgery) and in non surgical pain (tendonitis, lower back pain, gout or sports injury). The goal of the research is to include a bilayer tablet formulation of etodoloac for rapid uptake and eventual rapid onset of action to relieve acute pain. Using various excipients, the extended discharge comprises is prepared by wet granulation. The formulation comprises of effective amount of active ingredient etodolac or salts thereof in combination with compressible powder, superdisintegrant and effervescent agent.*

Keywords--- *Analgesic, Anti-inflammatory, Etodolac, NSAID, Osteoarthritis, Rheumatoid arthritis.*

I. INTRODUCTION:

The chronic inflammatory condition of rheumatoid arthritis triggers the progressive deterioration of the bone and articular. It deals with systemic inflammation and tissue injury. Enabling the inflammatory immune response at night allows early morning symptoms to deteriorate, resulting in discontinuity and consistency sleep disruption [1]. Symptoms are usually consistent with physical weakness and joint pain in the morning.

Osteoarthritis (OA) has 22 percent to 39 percent prevalence in India as the most common joint disease [2]. This occurrence is higher than many well known diseases such as AIDS, diabetes and cancer. The symptom of OA is always discomfort, frequently aggravated by joint use and usually relieved by rest [3]. OA flare-up happens with non-steroidal anti-inflammatory drugs (NSAIDs) following routine preventive treatment. The cause of the OA flareup is not known, although the dose or site of maintenance therapy may involve some transient pathophysiological changes. A painful flare-Up can show OA is not being optimally managed, or it can indicate a specific process such as avascular necrosis, crystalline arthritis and subchondral fracture [4]. Therefore, it may be necessary to remove the analgesic drug from the medication type immediately in patients who experience inadequately-relieved symptoms (severe and acute pain typically lasts less than 3-5 months), for example OA flare-ups with conventional NSAIDs[5]. The effect of rheumatoid

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arthritis (RA) in the United States is nearly 1.5 million. Women are 2-3 times more common than men in RA. RA signs include weakness, morning rigidity, joint stiffness, low-grade fever, joint pain, minor joint inflammation, numbness and tingling [6].

Multiple modalities for the diagnosis of OA and RA were also prescribed. Etodolac, a pyranocarboxylic acid, is an NSAID that prevents the development of arachidonic acid endoperoxides in prostaglandin, and is both effective and safe in the treatment of patients with OA relative to diclofenac sodium, naproxen, nabumetone and piroxicam [7]. For urgent pain relief in adults but not infants, Etodolac is approved by the Food and Drug Administration of the United States. The analgesic potency of etodolac 200 mg is equivalent to paracetamol 600 mg plus 60 mg of codeine and etodolac 400 mg to a latter combination[8]. The analgesic duration of etodolac (300 mg) is greater than paracetamol l[9]. Etodolac possesses a more favorable therapeutic index between anti-inflammatory effects and gastric irritation as compared to other NSAIDs[10]. A central action on the hypothalamus, which results in peripheral dilation and decreased cutaneous blood flow and consequent heat loss, can be caused by etodolac antipyretic activity. Etodolac shows binding affinity to plasma proteins (99% protein binding) and undergoes extensive metabolism in the liver[11]. Interestingly, etodolac displayed 80% oral bioavailability with good absorption profile in addition to half life of 4-7 hours[12]. Interestingly, etodolac is lipophilic (log P~2.5) in nature and displays low solubility in aqueous phase (16 mg/L)[13]. Therefore, two forms of etodolac dosage range have been prescribed by doctors, i.e. immediate release of the etodolac tablet of 200 mg-mg per 6 to 8 hours, with a maximum extended dose of 400 mg-mg once a day. To preserve its plasma level, the maximum dosage of etodolac does not exceed 1200 mg a day [14]. However, pharmacokinetic analysis of immediate release etodolac indicated that drug achieved maximum concentration in 1.7± 1.3 h (Tmax) while extended release tablet showed its Tmax at 7.8±3.2 h. Also, the Cmax of immediate release etodolac tablet is 20.8±6.7µg/ml. as compared to 11.9±4.1µg/ml of etodolac extended release tablet[6], [15]. This justified that immediate release of etodolac may provide the relief from acute pain and however; the duration of analgesic effect would be limited. On the other hand, extended release etodolac may assure long-lasting analgesic effect; however it would not provide instant analgesic effect.

I.I. Edotolac

The non-steroidal anti-inflammatory drug Etodolac (ETD) is used to relieve the underlying effects of rheumatoid arthritis through the modulations of cyclooxygenase mechanisms and other inflammatory mediators[15]. ETD is a specific COX-2 inhibitor which inhibits only cyclo-oxygenase-2 mediators and fewer gastrointestinal complications than most other NSAIDs.[6]. It is marketed as oral immediate release tablets or capsules, extended release tablets and conventional topical formulations. Chemically, it is "(RS)-2-(1, 8-Diethyl-4, 9-dihydro-3H-pyrano[3,4-b]indol-1-yl) acetic acid". For diagnosis of acute pain, Etodolac is approved in adults, but not in children by the US Food and Drug Administration (FDA).[16]. The diagnosis of symptoms and signs of osteoarthritis, rheumatoid arthritis and pain control is eligible for Etodolac. The standard dosage scheme in two or four split doses is 800 mg to 1200 mg [17]. This scheme may create enforcement problems due to the patient's lack of comfort. However, continued release mechanisms for drug delivery produce steady amounts of therapeutic active ingredients in contrast with variations in a traditional formulation at several doses[18]. Production of a 24-hour and/or once - a-day, continuous etodolac release formula

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presents problems due to the very poor aqueous solubility of Etodolac which is pH-independent below pH 3. For increasing pH up to 5 the solubility slowly increases, and with increasing pH up to 7 linearly increases.

II. MATERIALS AND METHODOLOGY

II.I. Materials

Etodolac, Microcrystalline cellulose, Crospovidone, Citric acid, Calcium carbonate, Hydroxypropylmethyl cellulose, Ethyl cellulose, Mannitol, Dibasic sodium phosphate, Starch paste 10%, Magnessium stearate, Talc.

II.II. Formulation preparation and design of Etodolac bilayer tablets

Specific techniques have been used in preparation of tablets from Bilayer, including Oros ® Push Pull technology[20], EN SO TROL Technology [21], L-OROS Technology[20], DUROS Technology[20] and DUREDAS™ Technology [21]. Etodolac has been added in the prescribed dose as one-time dose of the multiple divided dose therapy which is 400 mg b.i.d. or t.i.d. The ingredients were mixed together along with compressible powder, microcrystalline cellulose that allows direct compression of the tablet mixture. Table 1 displays the engineered composition of the bilayer tablet's immediate release level.

Table 1: Optimized composition of rapid release layer of etodolac bilayer tablet

Sr. No.	Ingredients	Quantity (mg)
1.	Etodolac	400
2.	Microcrystalline cellulose	75
3.	Crospovidone	65
4.	Citric acid	35
5.	Calcium carbonate	115

Granules were prepared using the wet granulation cycle for an extended release layer of the bilayer tablet [22]. The amount of etodolac added was the dosage needed for sustaining a long-term plasma level. Polymers hydroxypropylmethylcellulose and ethyl cellulose were added to control the drug release. Dibasic sodium phosphate was added to impart an alkaline microenvironment to the dosage form and minimized the pH solubility dependency of the etodolac as it passes through the gastrointestinal tract. The optimized composition of etodolac extended release layer is shown in **Table 2**. The bilayer tablet of etodolac was prepared at laboratory scale by compressing each layer separately to form the compacts which were further compressed together to form the bilayer tablet.

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Table 2: Optimized composition of extended release layer of etodolac bilayer tablet.

Sr. No.	Ingredients	Quantity (mg)
1.	Etodolac	400
2.	Hydroxypropylmethyl cellulose	50
3.	Ethyl cellulose	50
4.	Mannitol	100
5.	Dibasic sodium phosphate	75
6.	Starch paste 10%	27.5
7.	Magnessium stearate	6.75
8.	Talc	6.75

III RESULTS: -

III.I Quality control test on the Etodolac tablets

The bilayer tablets of etodolac were tested under the both official and non-official tests as prescribed in Indian Pharmacopoeia (Indian Pharmacopoeia, 2014) such as friability test, weight variation test, dissolution test, drug content analysis, and hardness test.

III.II Variation test of weight

20 bilayer etodolac tablets were taken randomly, individually weighted and average weight measured for the variation of weight. The weight of each tablet was consequently adjusted to average weight and the error in percent was determined. "Not more than two tablet tablets should be beyond the 5 percent deviation limit permitted for tablets weighing 250 mg or more," according to the Indian Pharmacopoeia. Results indicated that no tablet was lying outside the allowed limit of deviation. Hence, bilayer tablets of etodolac have qualified the weight variation test.

III.III Hardness test

The hardness test was conducted on 5 tablets using the Pfizer Hardness measuring tool, followed by average hardness. The average hardness of bilayer tablet of etodolac was estimated to be 16.12 kg.

III.IV Friability test

20 tablets were weighted together for the friability test and inserted in a Roche Friability test apparatus that rotated at 25 to 35 rpm and decreased per rotation through 6 inches of space. Tablets were removed after 4 minutes, de-dusted and again weighed. Weight loss of 0.89% was noticed which lies in the allowed limit of 1% as specified in Indian Pharmacopoeia, 2014.

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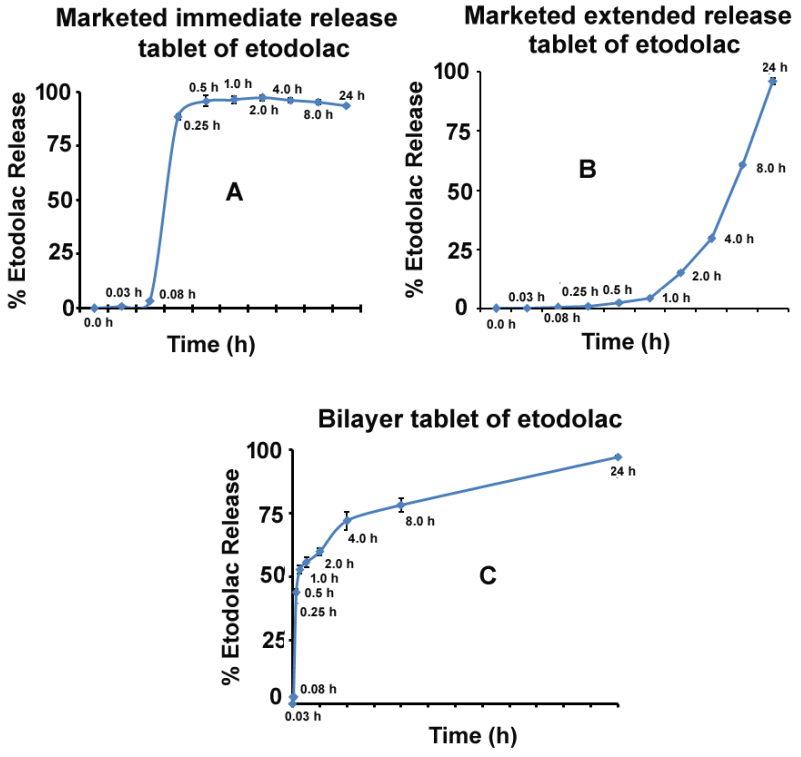
III.V Drug content analysis

Drug content analysis bilayer tablet of etodolac was carried out by using U.V/Visible spectrophotometry (Shimadzu 1800, Kyoto, Japan). In a pH7.2 phosphate buffer of 5-50 µg / ml (y=0.0256x + 0.0122 R2=0.998) a calibration curve of etodolac was developed. In the phosphate buffer pH 7.2 for examination, 3 bilayer etodolac tablets were taken, crushed and medicines were removed. The absorption of the filtered samples was determined from the height equation with 278.5 nm and the quantity of the etodlac. An average of 98.48% of etodolac was recovered from three tablets.

III.VI Dissolution test

A dissolution study was performed using USP dissolution study instruments type 2 on 5 bilayer etodolac tablets. As a dissolution medium held at 37 ° C and 50 rpm, around 900 ml simulated intestinal fluid (pH 6.8-7.2) has been taken as recommended to evaluate oral products for dissolution (Indian Pharmacopoeia 2014). A sample of 5 ml was taken and supplemented with a fresh dissolution to preserve sink conditions at the specified periods of time. The samples were processed through 0.22-µm (MDI, Ambala, India) membrane filter and the UV / Visible Spectrophotometer was used for measuring the filter's absorption by 278.5 nm. Data of dissolution testing of bilayer tablet of etodolac indicated 800 mg etodoolac containing bilayer tablet released 52.99±1.54% of drug in 0.5hr as compared to 95.97±2.61% of the etodolac released by marketed immediate release tablet containing 400 mg of etodolac. Furthermore, bilayer tablet of etodolac (~800 mg of etodolac) released 97.38±0.48% of drug at 24 h. On the hand, marketed extended release tablet of etodolac (~400 mg of etodolac) released 2.66±0.04% of drug at 0.5 h and 96.15±1.47% of etodolac at 24 h (Figure 1 A-C).



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In this way, data of comparative dissolution testing indicated that the dissolution profile of bilayer tablet of etodolac was comparable to marketed immediate release tablet of etodolac as well as marketed extended release tablet of etodolac. Therefore, we may expect that immediate release of etodolac from bilayer tablet will promote rapid absorption of drug from the intestinal absorption window and subsequent quick onset of action in acute pain management while The extended release of etodolac will sustain drug plasma levels for a sustained period of time for chronic pain management.

III.VII Storage condition

The etodolac bilayer tablet should be stored at 68°F to 77°F or 20-25°C in an airtight container or Store at room temperature, in a dry place. Protect the etodolac bilayer tablet from sunlight and moisture.

IV. CONCLUSION: -

The present study confirmed the development and optimization of etodolac bilayer tablets. Therefore, we can wrap up that currently available tablet or capsulate dosage forms of etodolac will either exhibit quick onset of action owing to immediate release or prolonged analgesic effect due to extended release. Hence the present etodolac tablets could simultaneously exhibit both quick analgesic action and maintain it for longer period of time.

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