A NOVEL FORMULATION DESIGN FOR EXTENDED RELEASE TABLET OF ETODOLAC FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

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Abstract

This study was aimed formulate of an extended-release tablet of Etodolac for the disease Rheumatoid arthritis were prepared by using different excipient like HPMC, Carbapol, Magnesium Stearate, MCC, at different concentrations. The wavelength of Etodolac 277nm. In precompression Study Powdered drug were evaluated for Angle of repose (36.42º- 42.01º), Bulk Density (0.19 - 0.25) g/mL and Tapped density (0.23-0.29) g/mL and compressibility index (13.79- 27.58). The results obtained were found to be satisfactory and within the specified limits. After compression parameters like Thickness, Hardness, Weight variation, Friability and *In Vitro* drug release studies were evaluated. In the present study the effect of types and concentration of polymer were studied on *In-Vitro* drug release. It shows that increase in concentration of polymer results in the extended drug release for 24 hours. In present studies, formulation containing Carbapol is probably showing release up to 94.55% drug release within 24hrs.

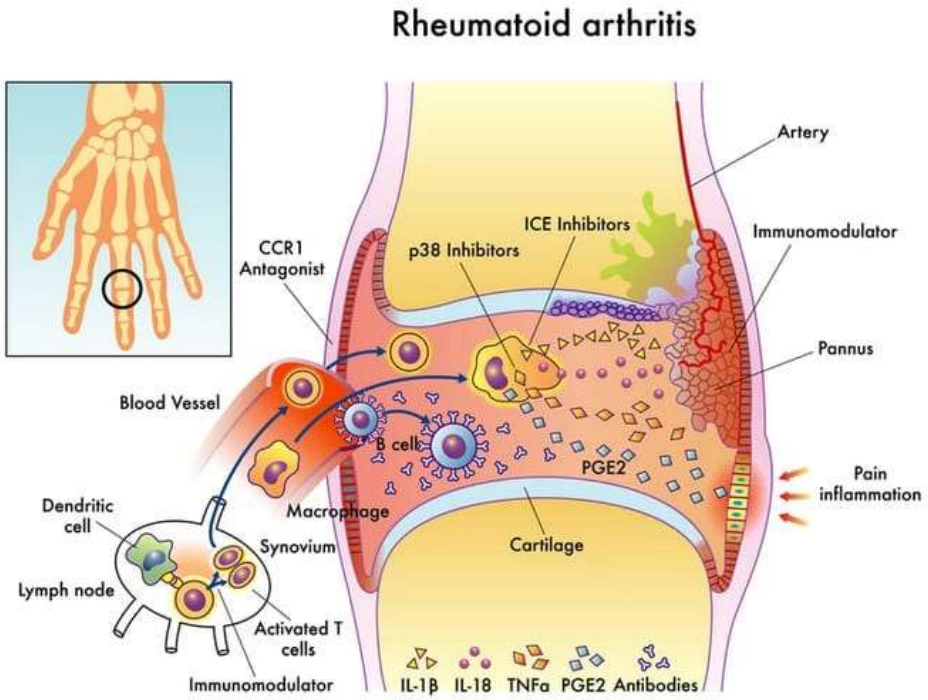
Keywords: Etodolac, Extended Release, HPMC, MCC, Direct Compression

INTRODUCTION

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years. Early modified release products were often intramuscular/subcutaneous injections of suspensions of insoluble drug complexes, e.g., procaine penicillin, protamine zinc insulin, insulin zinc suspensions or injections of the drug in oil, e.g., fluphenazine decanoate. Advances in technology have resulted in novel oral modified-release dosage forms. Many terms are used to describe modified-release products including extended-release, prolonged-release, controlled-release, controlled-delivery, slow release and sustained-release. Delayed-release Products are modified-release, but they are not extended-release by definition [1-3]. They entail the release of a discrete amount(s) of medicament after it has been administered. e.g., Enteric-coated products, have a lag time in which little or no absorption takes place. While there are a variety of modified-release pharmaceuticals available as prescription and over-the-counter medications, only a small number have been proved to provide a therapeutic benefit. Rather for being designed for clinical benefit, several of the formulations appear to have been devised to extend patents or give a marketing advantage over conventional-release medications. The term "arthritis" literally means "inflammation of the joints." Arthritis typically affects the joints, but it can also damage the surrounding muscles and connective tissues. Arthritis is caused by injuries, immune system problems, joint wear and tear, infections, or hereditary predisposition. Rheumatoid arthritis is a chronic, inflammatory autoimmune disease in which the body's immune system attacks the joints [4-6]. It's a debilitating and painful inflammatory disorder that can cause significant joint degeneration and mobility loss. Rheumatoid arthritis is a systemic illness that affects the skin, blood vessels, heart, lungs, and muscles, among other extraarticular tissues [7]. Rheumatoid arthritis causes pain, stiffness, warmth, redness, and swelling because the synovium, the joint lining, becomes inflamed. These inflammatory cells produce an enzyme that has the potential to breakdown cartilage and bone. A fine tissue layer up to three cells thick and a loosely distributed stroma containing connective tissue, microvasculature,

and lymphatics make up the normal synovial lining of diarthrodial joints. The main pathogenic characteristic of rheumatoid arthritis is inflammatory synovitis. Synovial hyperplasia, inflammatory cell infiltration, and vascularity are all features of this condition [8-12]. Edema and fibrin deposition are the most common symptoms at first. Synovial liner layer hyperplasia occurs as a result, involving macrophages and fibroblast-like synoviocytes. T.lymphocytes, B cells, macrophages, and plasma cells infiltrate the subliming layer, resulting in hyperplasia. Rheumatoid arthritis is caused by a variety of pathogenic causes. Etodolac's anti-inflammatory properties are due to suppression of the enzyme cyclooxygenase, which is similar to that of other NSAIDs (COX). This lowers the production of peripheral prostaglandins, which play a role in inflammatory mediation [13-15]. Etodolac binds to the upper region of the COX enzyme active site, preventing arachidonic acid, the enzyme's substrate, from entering. Etodolac was once assumed to be a non-selective COX inhibitor, however it has since been discovered to be 5–50 times more selective for COX-2 than COX-1. Antipyresis can be caused by central hypothalamic activation, which causes peripheral dilatation, increased cutaneous blood flow, and heat loss [16,17].

Figure 1: The Pathophysiology of Rheumatoid Arthritis



MATERIALS AND METHOD

Materials:

The drug Etodolac was obtained as a gift sample from Ralington pharma LLP (India) Ahmadabad. MCC, Carbopol 934, HPMC, Talc, magnesium Stearate was purchased from Merck Specialities Pvt. Ltd.

Method:

- Except pure drug Etodolac, all other ingredients were precisely weighted tale and magnesium stearate.
- Prior to mixing, all materials are mixed properly.
- Transfer all ingredients to a glass mortar, except the Magnesium Stearate and talc, and triturate until uniformly combined.
- Finally, Tale and magnesium stearate were added to the mixture.
- The powder was then compacted into tablets on a tablet machine and punch a tablet.

Formulation of Etodolac Extended-Release tablet:

Micrometric Studies has been carried out for the Etodolac tablet based on the results it was concluded that the drug is suitable for direct compression method due to fine size and passable flow characteristics. So, the extended-release Etodolac tablet of was prepared by Direct compression technique.

Tablet 1: Composition of Etodolac Extended Release tablet

Sr.No.	Ingredient for tablet	F1 Mg	F2 Mg	F3 Mg	F4 Mg	F5 Mg
1	Etodolac	400	400	400	400	400
2	HPMC (1%)	1	2	--	--	1
3	Carbapol 934 (%)	--	--	1	2	1
4	Talc (mg)	5	5	5	5	5
5	Magnesium Stearate (mg)	5	5	5	5	5
6	MCC (mg)	86	82	86	82	82

RESULTS AND DISCUSSION

Preformulation studies:

Characterizations of drug:

Table 2: Characteristics of drug

Test	Specifications	Observed
Description	White powder	White powder
Melting Point	145-148^{o}C	145^{o}C

Drug identification by FT-IR Spectroscopy:

Drug excipient compatibility studies lay the foundation for designing a chemically stable formulation for chemical and commercial development. Drug excipient compatibility studies are conducted during Preformulation to select the most appropriate excipient compatibility studies are performed by FTIR studies.

Table 3: Drug identification by FT-IR Spectroscopy

SR.NO	Formulation	C=O Region (Cm^{-1})	N-H Streching (Cm^{-1})	O-H Streching (Cm^{-1})
1	Etodolac	1741.98	3423.17	3760
2	Etodolac+HPMC	1736.94	3346.11	3743.74
3	Etodolac+Carbapol	1742.94	3349.16	3712.02

Figure 2: FT-IR graph of Etodolac

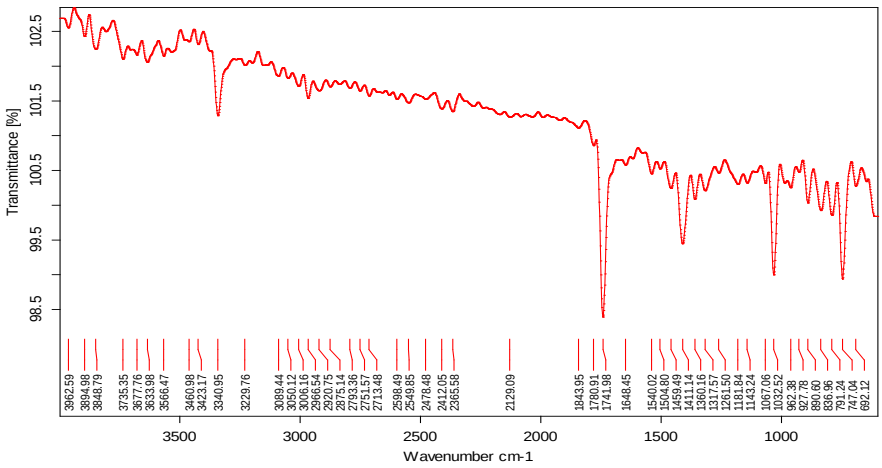
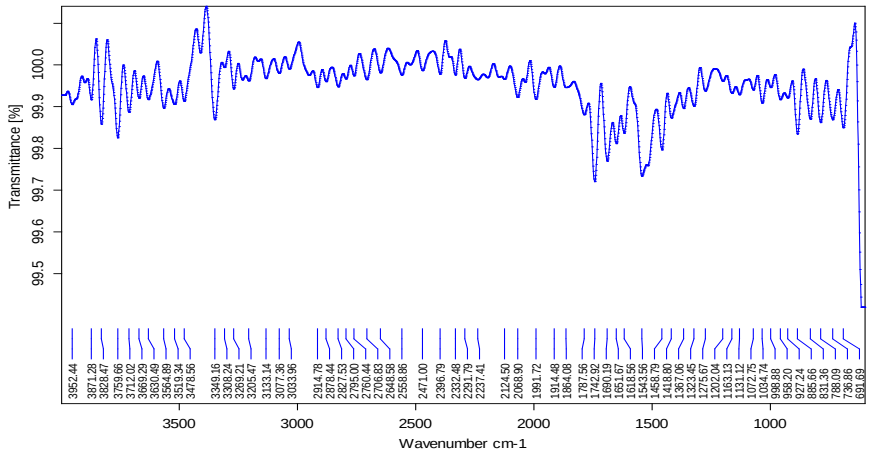


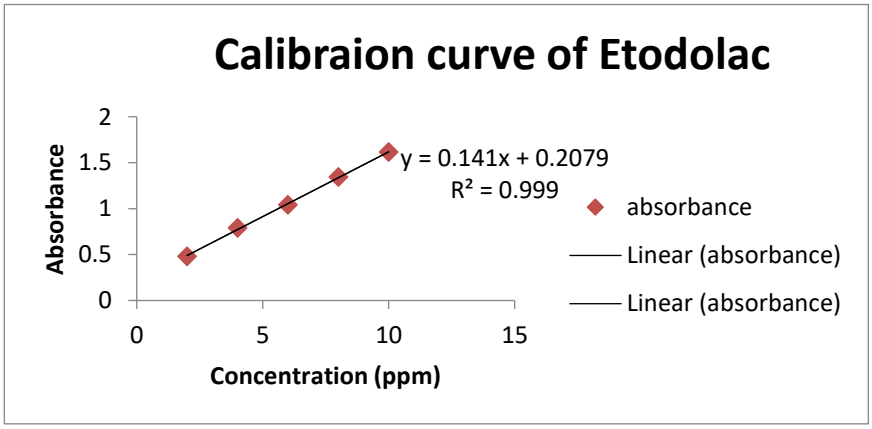
Figure 3: FT-IR graph of Etodolac + Carbapol



Construction of calibration curve:

The calibration curve of etodolac was obtained in phosphate buffer pH 7.4 by plotting absorbance Vs. Concentration shown in fig.4. These reading shown in in the below table. The calibration curve of etodolac shows the correlation coefficient of 0.9992. The curve was found to be linear in the concentration range of 2-10µg/ml at 226nm. These readings are shown in figure 4.

Figure 4: Calibration curve



Solubility:

Table 4: Solubility and absorbance of drug under the UV Spectrophotometer

Sample	Absorbance(λmax=277nm)
DMSO	0.3112
PEG	0.5756
Chloroform	0.4215
Methanol	0.9789
Water	0.2815

Figure 5: Graph of solubility absorbance of Etodolac

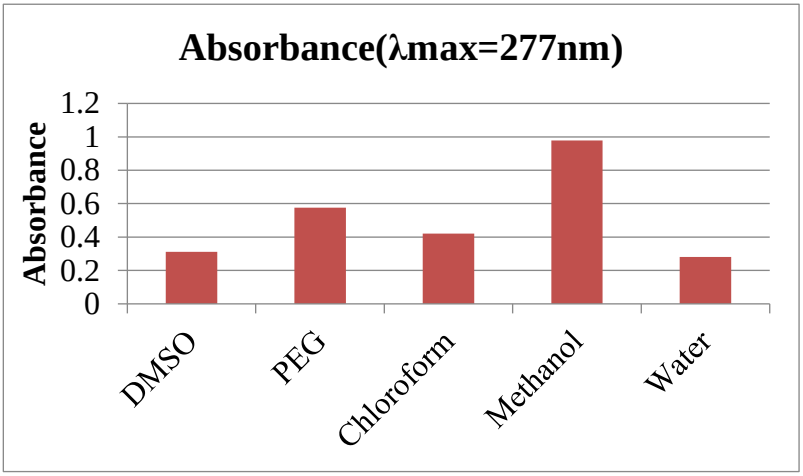
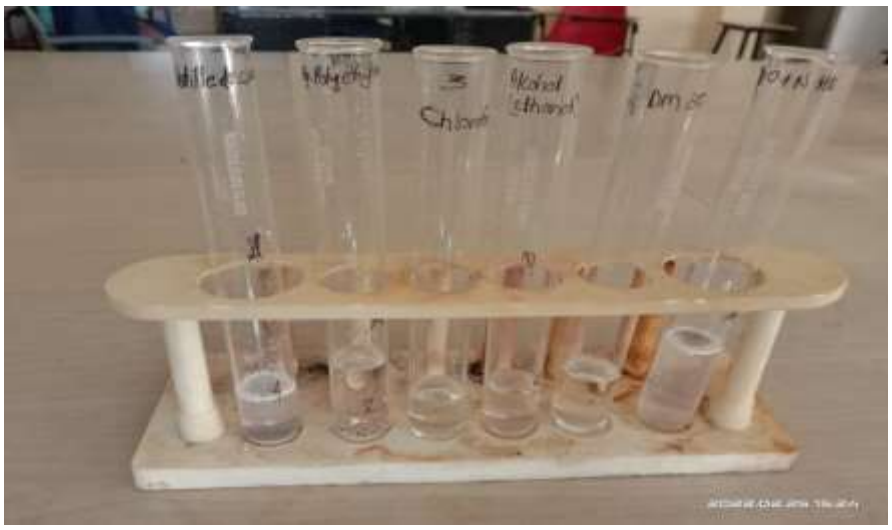


Figure 6: Solubility of Etodolac in the laboratory under UV Spectrophotometer



Post Compression Studies

Hardness:

- Hardness test for tablet is used to determine the breaking point and structural integrity of the tablet. It is also used to find out how tablet changes under the conditions of storage, transportation, packaging and handling before usage.
- We have taken Monsanto hardness tester.
- Measure the thickness of the tablet.
- Put the tablet into the socket.
- Tighten the piston of the hardness tester until tablet broken off.
- Measure the weight on the tester when tablet were broken.

Thickness

Tablet thickness is an important Quality Control test for tablet packaging. The thickness of tablet is therapeutic effectiveness of tablet. A vernier calliper, is used to measure tablet thickness.

Depending on the size of the tablet, the thickness should be managed within a 5% fluctuation of a specified value.

Diameter

The diameter of tablet is an important parameter and very important for increasing the patient compliance. This test is also helpful to prevent patient confusion about medication dose.

Friability

The friability of all the formulation batches of etodolac was found to be below 1%.

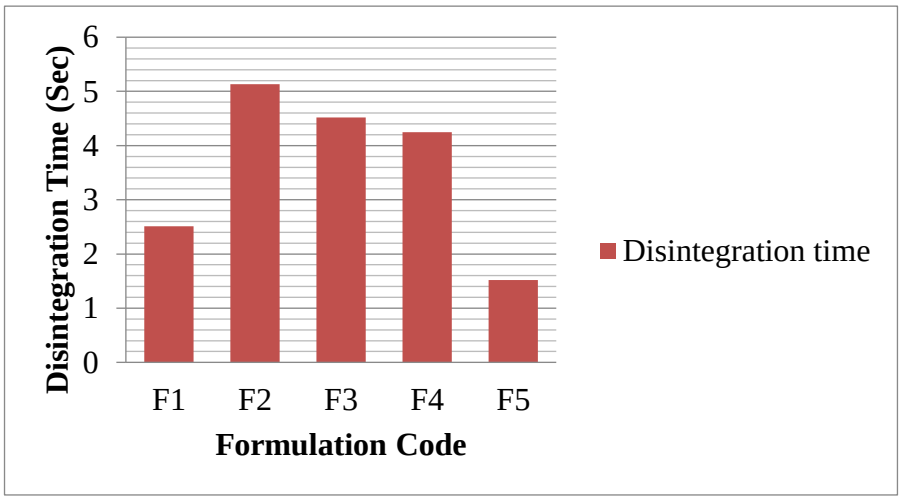
Uniformity of weight

Uniformity of weight of prepared tablets was found within the specification of Indian Pharmacopoeia.

Disintegration Time

All the batches of extended-release tablet for each formulation were found to be disintegrate less than 2.5-10 minutes. The graphical representation of as shown in figure 7.

Figure 7: Disintegration time



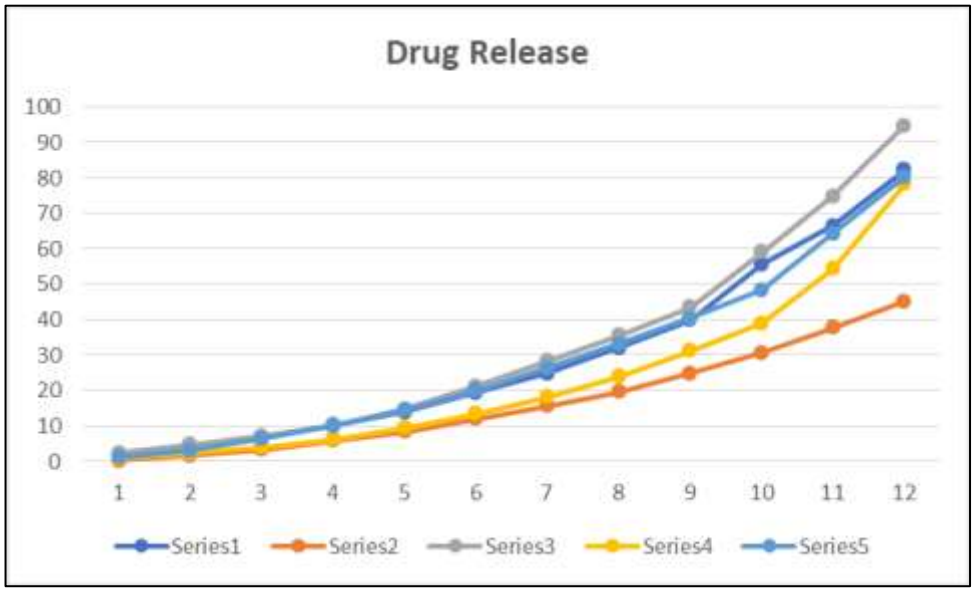
In-vitro drug release

In-vitro drug release of the prepared extended release tablet was performed in the pH 7.4 using USP type-II/IP-I dissolution apparatus. The *In-vitro* drug release of all the formulation results were mentioned in the table. The results are shows that the release profile of F3 formulation contain carbapol was found to have maximum release 94.55% at the end of 330 minutes. *In-vitro* release of all formulations was graphically represented as shown in figure 8.

Tablet 5: Dissolution profile of Etodolac Extended-Release Tablet.

Time in Hours	F1	F2	F3	F4	F5
1	1.186857	0.099769	2.284321	0.645708	1.087088
3	3.606864	1.572366	4.65165	2.242018	2.952377
5	6.760376	3.257272	7.068464	3.990777	6.285474
7	10.11023	5.674087	9.990511	6.082742	9.95619
9	13.82086	8.359879	14.69005	9.376729	14.44103
11	19.2539	11.93242	21.06651	13.2837	19.88365
12	24.78672	15.51774	28.17728	18.06385	26.13241
14	31.9318	19.45584	35.34072	23.88161	33.0149
16	39.68429	24.68455	43.31589	31.00035	40.22543
18	55.50612	30.53024	58.89748	38.81589	48.17666
20	66.38338	37.67852	74.61236	54.20513	64.11981
22	82.04239	45.03193	91.55427	78.13861	80.07414
24	85.04239	60.03193	94.55427	82.13861	84.07414

Figure 8: Percentage drug release for Formulation F1-F5



CONCLUSION

The formulation of an extended-release tablet of Etodolac for the disease Rheumatoid arthritis were prepared by using different excipient like HPMC, Carbapol, Magnesium Stearate, MCC, at different concentrations. These tablets were prepared by using direct compression method. Preformulation studies are carried out to find the different physiochemical properties of the drug which help to identify basic properties of drug. Under the preformulation studies solubility, melting point, UV spectroscopy, FT-IR studies are carried out. The drug is highly soluble in methanol with absorbance of 0.9789. The wavelength of etodolac

277nm. In precompression Study Powdered drug were evaluated for Angle of repose (36.42º- 42.01º), Bulk Density (0.19 - 0.25) g/mL and Tapped density (0.23-0.29) g/mL and compressibility index (13.79- 27.58). The results obtained were found to be satisfactory and within the specified limits. After compression parameters like Thickness, Hardness, Weight variation, Friability and *In Vitro* release studies were evaluated. In the present study the effect of types and concentration of polymer were studied on *In-Vitro* drug release. It shows that increase in concentration of polymer results in the extended drug release for 24 hours. In present studies, formulation containing Carbapol is probably showing release up to 94.55% drug release within 24 hrs. According to stability study it was found that there was no significant change in hardness, drug content and *in vitro* dissolution of optimized formulation (F3).

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