



CODEN [USA]: IAJPBB

ISSN : 2349-7750

## INDO AMERICAN JOURNAL OF PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

<http://doi.org/10.5281/zenodo.4463331>
Available online at: <http://www.iajps.com>

Research Article

# FORMULATION AND EVALUATION OF SOLID LIPID MICROPARTICLES OF ETORICOXIB IN GRAPHENE OXIDE FOR EFFECTIVE TREATMENT OF RHEUMATOID ARTHRITIS

Vivek Kumar Bihania<sup>1\*</sup>, Ashutosh Badola<sup>2</sup>

<sup>1</sup>School Of Pharmaceutical Sciences, Shri Guru Ram Rai University, Patel Nagar Dehradun,  
Uttarakhand, India.

Article Received: November 2020    Accepted: December 2020    Published: January 2021

**Abstract:**

*Etoricoxib has been in use for treatment of Rheumatoid arthritis for several years. In study, the microparticles are prepared of etoricoxib loaded in graphene oxide & transmitted through intra-articular administration in joint cavity. The absorbance maxima of the test drug in ethanol were observed at 284µm which perfectly matched the standard value given in E.P It was observed that the test drug is freely soluble in ethanol, methanol and soluble in phosphate buffer pH 7.4 Modified solvent evaporation technique was selected due to easy recovery of particles and on evaluation of particle size they were found in Micro range. pH of the prepared Microparticle was found to be 7.54 which is in blood buffer range. The % cumulative release of the prepared formulations is given as ET4 98.61% (1:2 drug: carrier ratio) > ET2 97.57% (1:3) > ET5 96.34% (1:3) > ET6 95.27% (1:4) > ET3 94.8% (1:5) > ET1 93.33% (1:6). A burst release was not observed for any of the formulations, this may be due to better entrapment of drug into carrier matrix. From the observed values it may be concluded that release rate of the drug not solely depends on carrier concentration but also a texture, loading capacity and surface morphology. After comparing different evaluation parameters like percentage yield, particle size, zeta potential. PDI, percentage entrapment efficiency and in-vitro diffusion study ET4 was selected as the best optimized formulation. The particle size of the formulation ET4 was reported as 18.1µm, percentage yield as 57%, zeta potential as -18.2 within 96.5%, PDI as 0.248. % entrapment efficiency as 99.36% and in-vitro diffusion as 98.41% in study period. Hence, it was concluded that formulation ET4 can be used for further study.*

**Corresponding author:****Vivek Kumar Bihania,**

School Of Pharmaceutical Sciences, Shri Guru Ram Rai University,  
Patel Nagar Dehradun, Uttarakhand, India.

QR code



Please cite this article in press Vivek Kumar Bihania *et al*, *Formulation and evaluation of solid lipid microparticles of Etoricoxib in Graphene oxide for effective treatment of Rheumatoid arthritis.*, *Indo Am. J. P. Sci.*, 2021; 08(1).

**INTRODUCTION:****Microparticle:**

The “micro” has found in last decade a growing application to different fields of the facts. Micro science, micro technology, micro materials or micro chemistry are only a few of the new micro-containing terms that occur frequently in scientific reports, in popular books as well as in newspapers and that have become memorable to a wide public, even of non-experts. The prefix came from the ancient Greek *μᾶνος* through the Latin *Nanos* significance literally dwarf and by lean-to, very tiny. By the convention of international System of Units (SI) it is used to indicate a reduction factor of 10<sup>9</sup> times. So, the micro sized world is typically measured in micrometres (1 μm corresponding to 10<sup>6</sup> μm) and it encompasses systems whose size is on top of molecular proportions and below macroscopic ones (generally > 1 μm and < 100 μm). [1]

Micro technology is the science of the small; the very small. It is the use and exploitation of matter at a tiny scale. By this size, atoms and molecules work another way, and provide an assortment of surprising and attractive uses. Micro technology and Micro science studies have emerged rapidly during the past years in a broad range of product domains. It provides opportunity for the development of materials, including those for medicinal applications, where conventional techniques may reach their limits. Micro technology should not be viewed as a single technique that only affects specific areas. Although often referred to as the ‘tiny science’, micro technology does not simply mean very small structures and products. Microscale features are often included into mass materials and bulky surfaces.[2] Microtechnology represent the design, production and purpose of materials at atomic, molecular and macromolecular scales, in order to produce new micro sized material Pharmaceutical Micro particle are defined as solid, submicron-sized (less than 100 μm in diameter) drug carrier that may or may not be biodegradable. The term micro particle is a collective name for both Micro particle and micro capsules. In uniformly dispersed manner drug availed in matrix system inside Micro particle, although micro capsules avail the drug is bounded by a inimitable carrier membrane.[3]

**Types of Micro particle:**

Two types formed as:

- i. Micro particle are solid core spherical particulate which enclose drug surrounded inside or wrapped up onto the surface (matrix type).

- ii. Micro capsule are vesicular system in which drug encapsulated inside the middle core enclosed in carrier sheath.[4]

**Rheumatoid arthritis:**

RA is an autoimmune disease. It is also a systemic disease, which means it affects the whole body. It occurs when a person's immune system mistakes the body's healthy tissues for foreign invaders. As the immune system responds, inflammation occurs in the target tissue or organ. In the case of RA, this can be the joints, lungs, eyes, and heart.

**Symptoms of RA include:**

Pain, swelling, and stiffness in more than one joint, Symmetrical joint involvement, Joint deformity, Unsteadiness when walking, A general feeling of being unwell, Fever, Loss of function and mobility, Weight loss, Weakness. According to the Centres for Disease Control and Prevention (CDC), the symptoms usually affect the same joints on both sides of the body Symptoms tend to come and go. During a remission, they can disappear, or they can be mild. However, during a flare, they can be severe. Etoricoxib is a synthetic, Nonsteroidal anti-inflammatory drug (NSAID) with antipyretic, analgesic, and potential antineoplastic properties. Etoricoxib specifically binds to and inhibits the enzyme cyclooxygenase-2 (COX-2), resulting in inhibition of the conversion of arachidonic acid into prostaglandins. Inhibition of COX-2 may induce apoptosis and inhibit tumour cell proliferation and angiogenesis.[5]

**Preformulation study related to preparation method and optimization:****Selection of Preparation method:**

Modified Micro precipitation, solvent evaporation and modified solvent evaporation techniques are some of the preparation techniques tried in the Preformulation level for the preparation of Etoricoxib loaded Micro particles. Modified micro precipitation, Ion gelation and solvent evaporation techniques were not selected due to difficulty in recovery of particles and agglomeration problems respectively. Modified solvent evaporation technique was selected due to easy recovery of particles and on evaluation of particle size they were found in Micro range.

**Selection of solvent:**

After the selection of preparation technique, solvent selection was carried out according and Method and carrier. Trials were conducted after the selection of solvent for optimization of rotation speed.

**Duration of rotation:**

In the first trial the rotation speed was kept 800-1200rpm and duration of rotation was the particle size was obtained as 185.4 $\mu$ m. In the second Chance rotation of 1800-2100rpm then particle size was obtained as 55.2 $\mu$ m. From the above observation, it was concluded that with increase in rotation speed the particle size decreases. Hence, the rotation speed was selected as 1800-2000rpm. [6]

#### Formulation table for preparation of Etoricoxib

##### Microparticle:

##### Method:

SLMs loaded with Etoricoxib were prepared using melt Emulsification and low-temperature Solidification method. Etoricoxib was dissolved in methanol and mixed with ethanol Solution containing PEG 400. The mixtures were sonicated for 15 minute, and then added drop wise to Span 80 %,  $\beta$ -cyclodextrin and Graphene solution, stirred at 2100 rpm for 0.3 h at 70 °C temperature. The mixed solution was transferred to icy water bath and stirring for four hour at 2000 rpm. Different formulations of drug loaded SLM were prepared by Varying concentrations of PEG 400 as shown in the below in table no.1 and these SLM dispersions used for further study.

S.No.	Ingredients	Formulations					
		ET1	ET2	ET3	ET4	ET5	ET6
1	Etoricoxib	50mg	50mg	50mg	50mg	50mg	50mg
2	Graphene oxide	200mg	150mg	250mg	100mg	150mg	300mg
3	$\beta$ -cyclodextrin	50mg	50mg	50mg	50mg	50mg	50mg
4	PEG 400	1ml	1.5ml	2ml	1ml	1.5ml	2ml
5	Ethanol	95ml	95ml	95ml	95ml	95ml	95ml
6	Methanol	5ml	5ml	5ml	5ml	5ml	5ml
7	Span 80(%w/v)	0.5ml	1ml	1.5ml	0.5ml	1ml	1.5ml

Table no. 1. Formulations of Etoricoxib Solid Lipid Microparticle in GO

#### Evaluation of Etoricoxib loaded Microparticles

##### Particle Size Determination:

Particle size of the test drug was determined using optical microscopic method. The maximum number of particles of test drug was found in the range 2 to 4 eyepiece division (Fig 5.1 & 5.2) and average particle size was found to be 32.8  $\mu$ m. For the efficient joints delivery the particle size of the drug needs to be in micro range. Thus, for joints targeting the reduction in particle size of the test drug is required.[7]

##### Percentage yield:

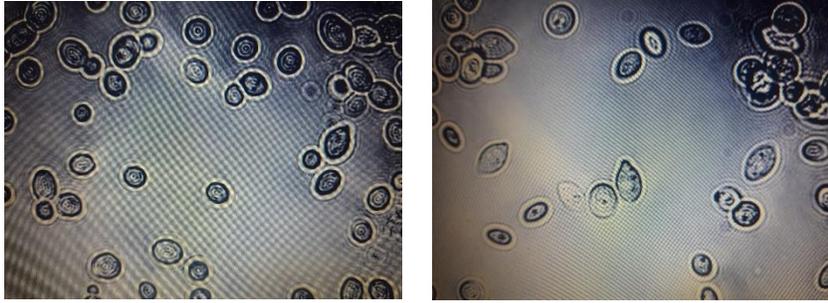
Percentage yield of the prepared micro formulations ET1 to ET6 were calculated and was found in between 35.60% to 63.52% respectively (Table no.2). A conclusion may be drawn from above data that with increase in carrier concentration percentage yield of the micro formulation increases.

Table no 2. Percentage yield of Etoricoxib Solid Lipid Microparticle in GO

S.No.	Formulation	Percentage yield ( $\pm$ SD)
1	ET1	43.02 $\pm$ 0.23
2	ET2	63.52 $\pm$ 0.35
3	ET3	47.25 $\pm$ 0.12
4	ET4	57.62 $\pm$ 0.33
5	ET5	35.60 $\pm$ 0.07
6	ET6	37.34 $\pm$ 0.25

**Particle size distribution:**

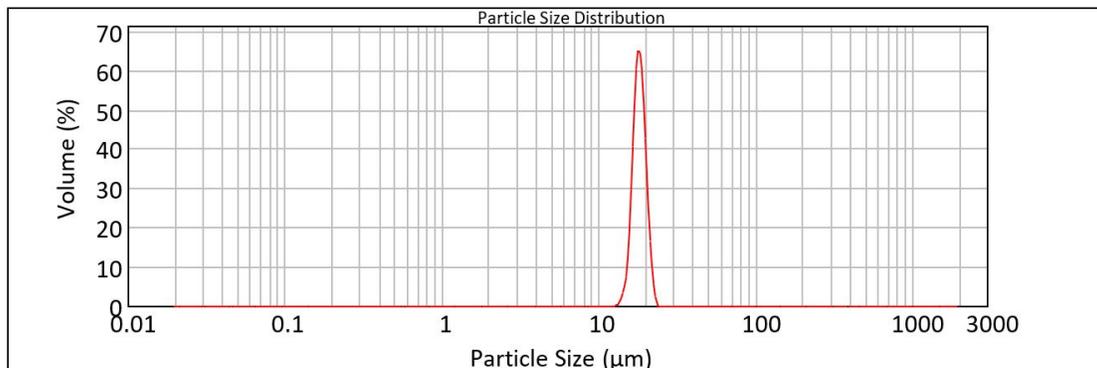
The particle size of prepared formulations was evaluated using triangular microscope & zetasizer. The particle size the prepared formulations ET1 to ET6 lied in a range. Formulation ET4 was found to have the optimum particle size i.e. 18 $\mu$ m from the above data it was observed that with increase in ratio of carrier, the particle size of the formulation increase.[8]



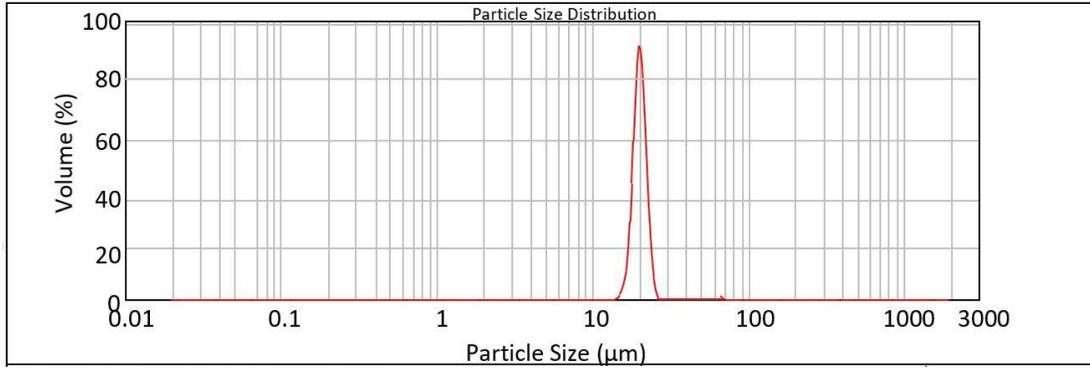
**Fig 1. Particle size of microparticles**

**Table no.3. Particle size of Etoricoxib Solid Lipid Microparticle in GO**

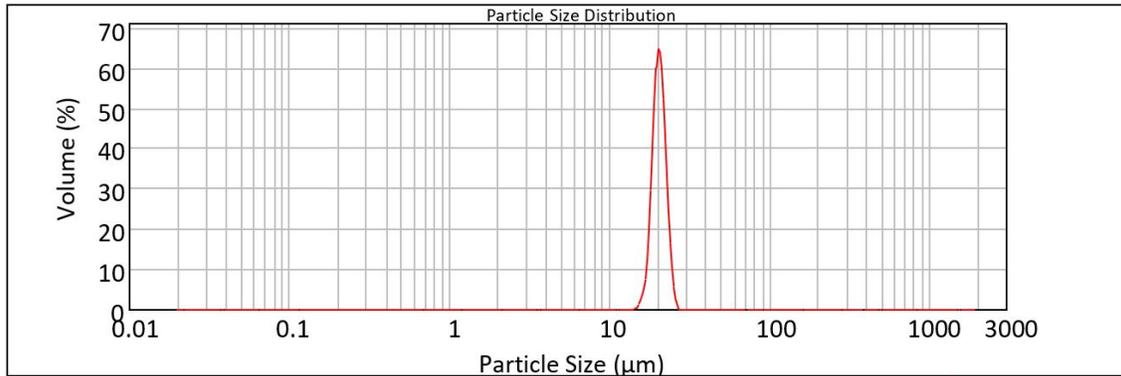
S.No.	Formulation	Particle size	
		Avg. Size ( $\mu$ m)	Volume (%)
1	ET1	14.2	63.5
2	ET2	19.2	93.7
3	ET3	21.3	67.2
4	ET4	18.2	96.3
5	ET5	56.3	65.3
6	ET 6	59.2	95.4



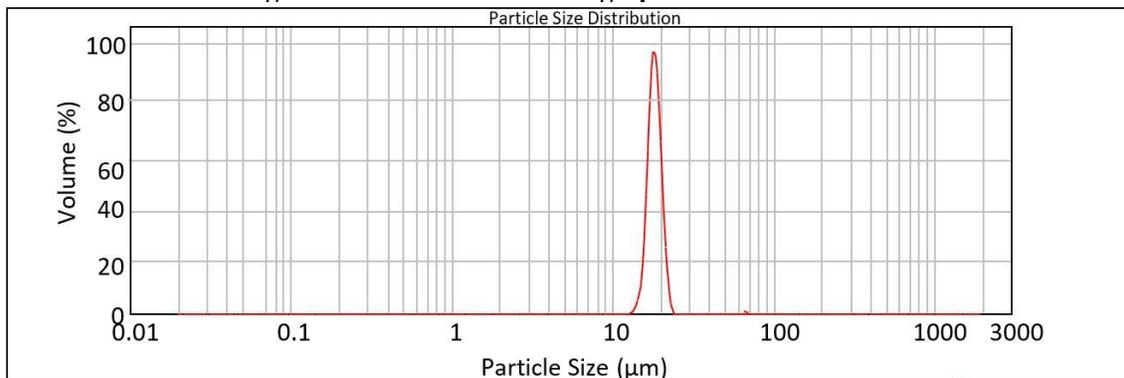
**Fig 2. Particle size Distribution graph of Formulation ET1**



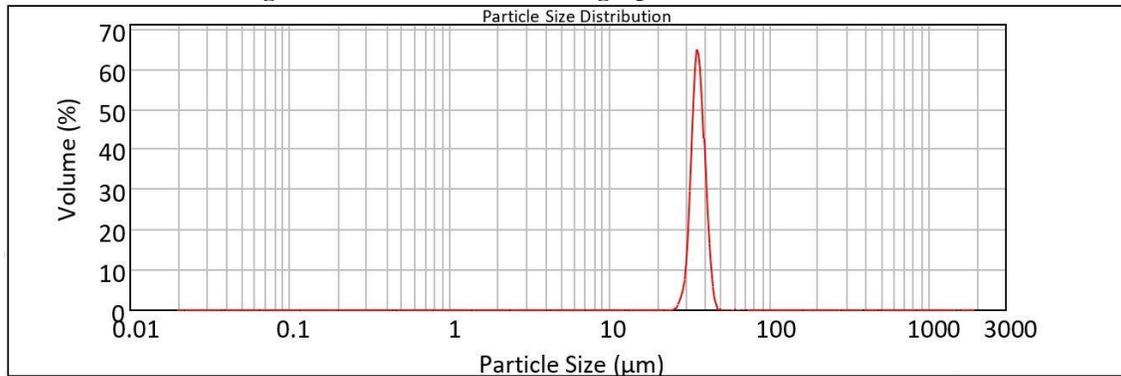
**Fig 3. Particle size Distribution graph of Formulation ET2**



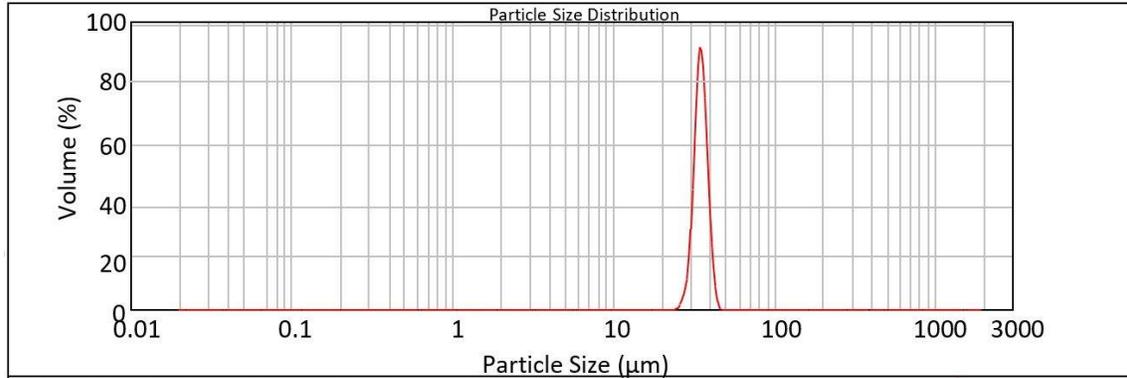
**Fig.4. Particle size Distribution graph of Formulation ET3**



**Fig.5. Particle size Distribution graph of Formulation ET4**



**Fig.6. Particle size Distribution graph of Formulation ET5**



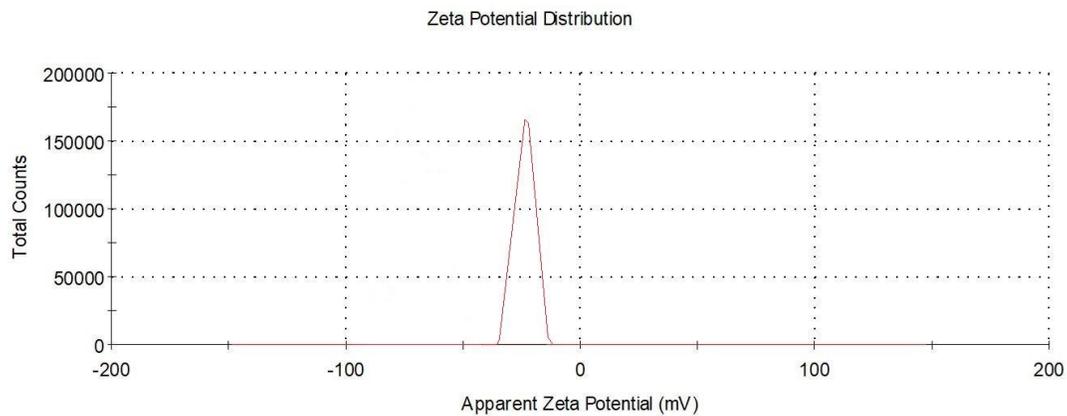
**Fig.7. Particle size Distribution graph of Formulation ET6**

#### Zeta potential Study:

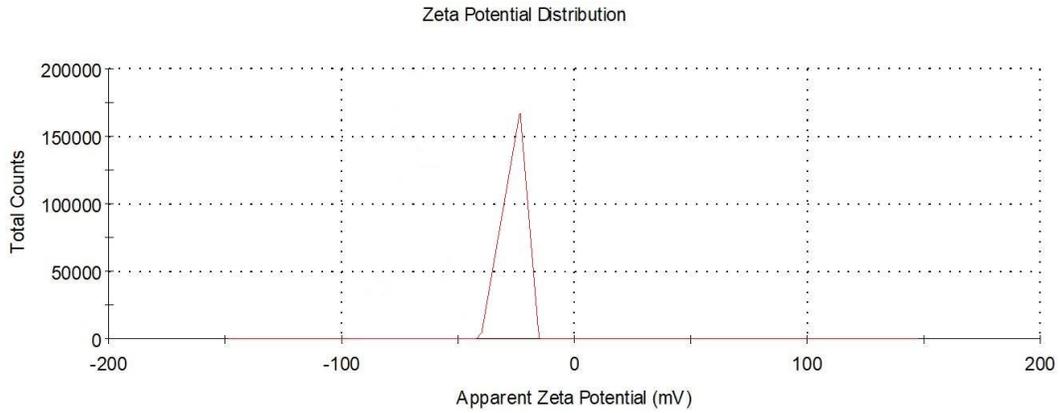
Zeta potential of the formulated microparticles was found between -18mV to -26 mV (Table no. 4 and Fig. no 8 to 13). As per the reports, micro formulations with a potential more than +25mV and less than -25mV are known to have high degree of stability and from the given data it was observed that the prepared micro formulations show model stability [9]

**Table no.4. Zeta potential of Etoricoxib Solid Lipid Microparticle in GO**

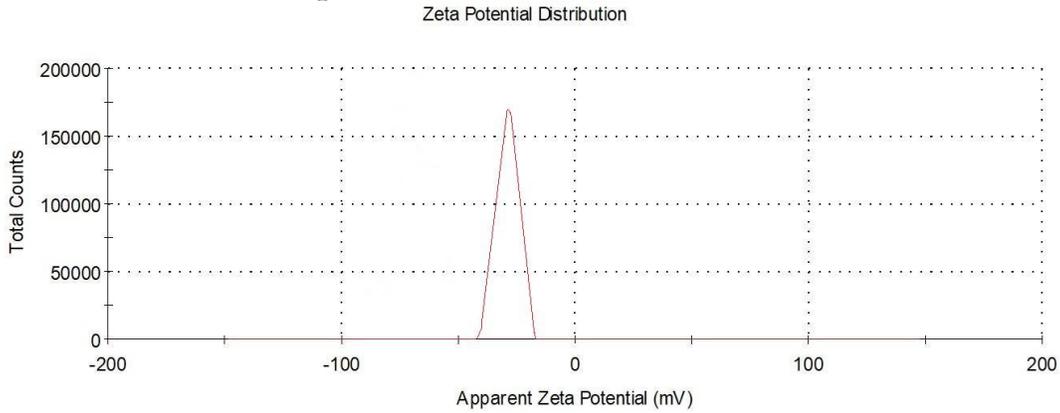
S.No.	Formulation	Zeta Potential (mV)
1	ET1	-24.7
2	ET2	-18.3
3	ET3	-24.8
4	ET4	-18.1
5	ET5	-26.7
6	ET6	-21.2



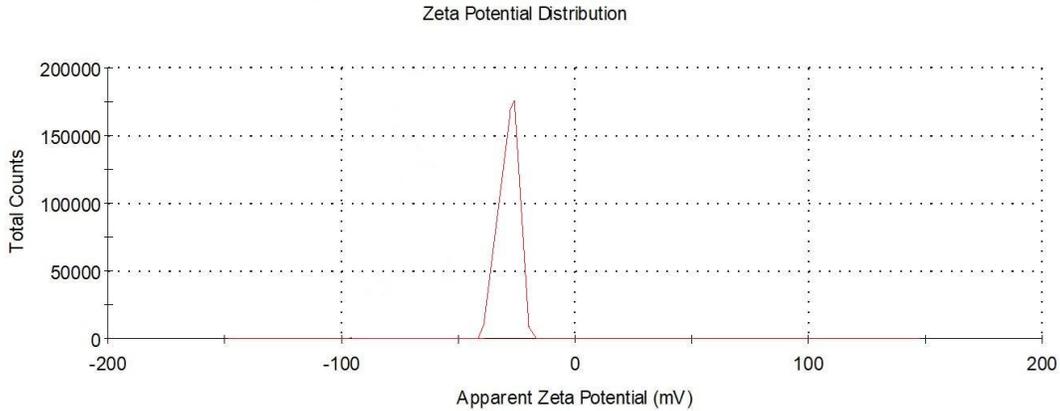
**Fig 8. Zeta Potential Distribution for ET1**



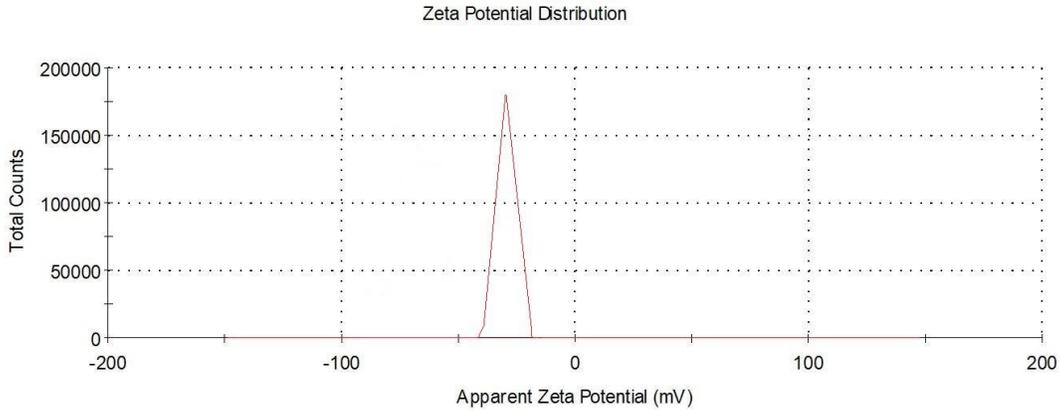
**Fig 9. Zeta Potential Distribution for ET2**



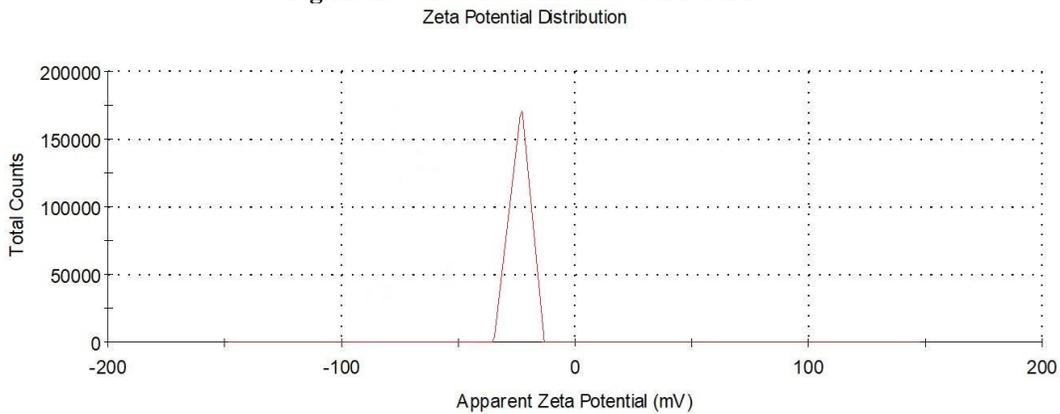
**Fig 10. Zeta Potential Distribution for ET3**



**Fig 11. Zeta Potential Distribution for ET4**



**Fig 12. Zeta Potential Distribution for ET5**



**Fig 13. Zeta Potential Distribution for ET6**

**Polydispersity index of prepared Etoricoxib Microparticle:**

The Polydispersity index data of the prepared formulation was given in Table no. and Fig, no.14. It was observed that all the formulations are mid-range Polydispersity. This is due to wide-ranging size distribution of the particles. There was no co-relation establishes between the ratio of carrier and PDI value of the prepared micro formulation. [10]

**Table no.5. Polydispersity index of Etoricoxib Solid Lipid Microparticle in GO**

S.No.	Formulation	Polydispersity Index
1	ET1	0.713
2	ET2	0.254
3	ET3	0.591
4	ET4	0.248
5	ET5	0.923
6	ET6	0.281

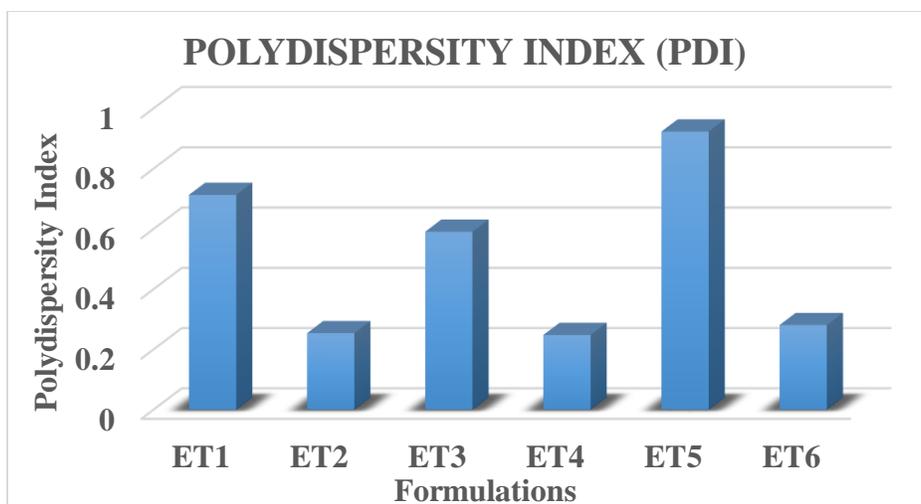


Fig. 14. PDI distribution graph of prepared Etoricoxib solid lipid Microparticle in GO

#### Evaluation of Surface entrapment and percentage entrapment efficiency:

The surface entrapment and % entrapment efficiency of the prepared formulations was reported in Table no.6. and fig. 15 to 16. From the given data it was observed that in between 0.64% 3.44% drug was present in the surface thus concluding the high percentage of drug entrapment within the carrier matrix. ET4 has the highest % entrapment efficiency 99.36% this may also be concluded that the surface entrapment of drug decreases with increase in Carrier concentration.[11]

Table no.6. Surface Entrapment and Drug Entrapment efficacy of Etoricoxib Solid Lipid Microparticle in GO

S.No.	Formulation	Surface Entrapment (%) $\pm$ SD	Drug Entrapment (%) $\pm$ SD
1	ET1	2.38 $\pm$ 0.14	97.62 $\pm$ 0.23
2	ET2	3.44 $\pm$ 0.08	96.56 $\pm$ 0.35
3	ET3	1.84 $\pm$ 0.23	98.16 $\pm$ 0.12
4	ET4	0.64 $\pm$ 0.11	99.36 $\pm$ 0.33
5	ET5	1.54 $\pm$ 0.09	98.46 $\pm$ 0.26
6	ET6	1.93 $\pm$ 0.23	98.07 $\pm$ 0.21

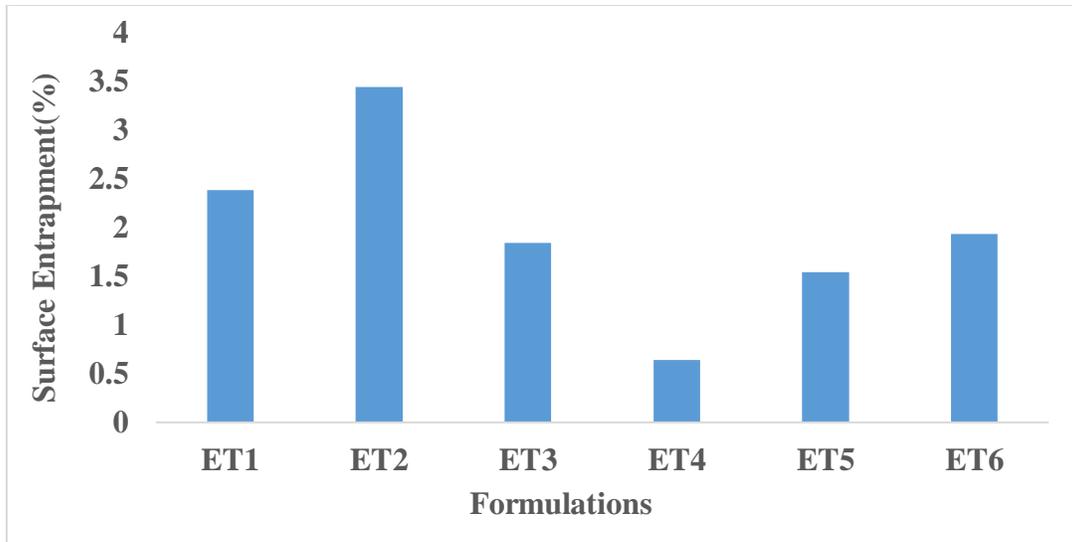


Fig 15. Surface Entrapment graph of Etoricoxib Solid Lipid Microparticle in GO

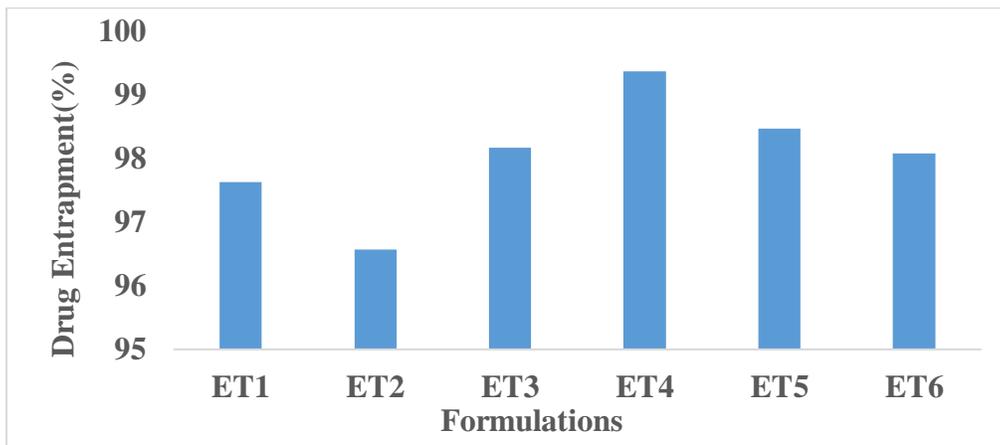


Fig 16. Drug Entrapment efficacy of Etoricoxib Solid Lipid Microparticle in GO

#### Evaluation of Etoricoxib loaded Microparticle:

##### pH study of prepared Microparticle:

pH of the prepared Microparticle was found to be 7.54 (fig.17). The observed value of pH lies within the range of physiological pH of the blood i.e. pH 7.4. Thus, suggesting no blood irritancy.



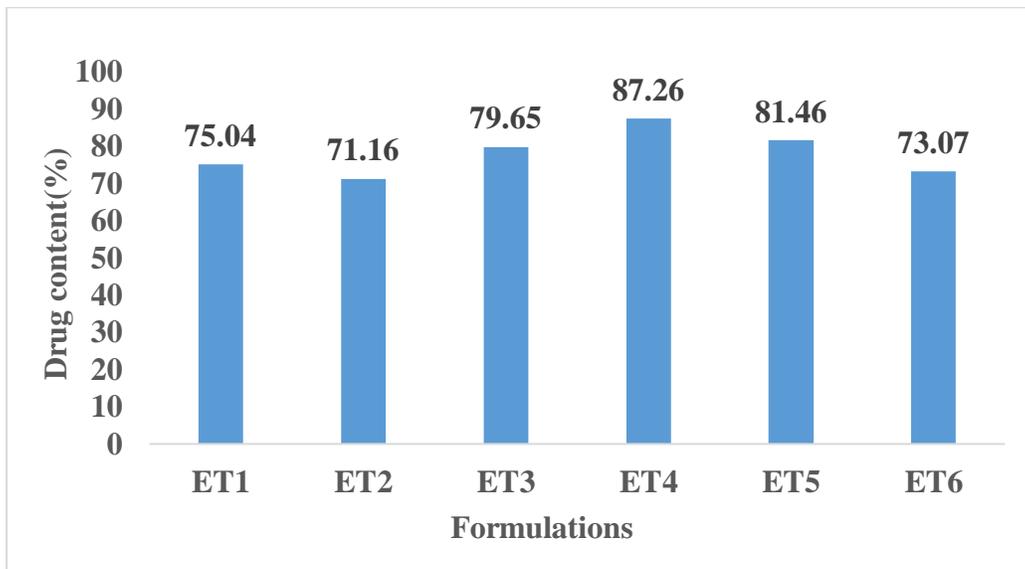
Fig 17. pH of prepared microparticles

**Evaluation of Drug content of prepared Microparticle:**

The drug content of the prepared formulation was reported in Table no.7.and Fig no.18. From experimental result it was observed that in maximum number of result formulation Percentage drug content was greater than 71.16%, which confirmed good drug loading capacity of prepared micro particles and from the study it may be concluded that % drug content of Microparticle depends on variability of preparation method.<sup>[12]</sup>

**Table no.7. Drug Content (%) of Etoricoxib Solid Lipid Microparticle in GO**

S.No.	Formulation	Drug Content (%) $\pm$ SD
1	ET1	75.04 $\pm$ 0.23
2	ET2	71.16 $\pm$ 0.35
3	ET3	79.65 $\pm$ 0.12
4	ET4	87.26 $\pm$ 0.33
5	ET5	81.46 $\pm$ 0.07
6	ET6	73.07 $\pm$ 0.25

**Fig 18. Drug content of Etoricoxib Solid Lipid Microparticle in GO****In -vitro diffusion study of Etoricoxib loaded Microparticle:**

The release data of the drug loaded Microparticle formulations was shown in Tables Fig.19. From the release data it was observed that more than 98.34 of drug was released in 6min. study period by all the formulations. It was also clearly observed that release rate and % CR are inversely proportional to carrier concentration with an increase in carrier concentration the release rate of the drug was retarded. The % cumulative release of the prepared formulations is

given as ET4 98.61% (1:2 drug: carrier ratio) > ET2 97.57% (1:3) > ET5 96.34% (1:3) > ET6 95.27% (1:4) > ET3 94.8% (1:5) > ET1 93.33% (1:6).

A burst release was not observed for any of the formulations, this may be due to better entrapment of drug into carrier matrix. From the observed values it may be concluded that release rate of the drug not solely depends on carrier concentration but also a texture, loading capacity and surface morphology.

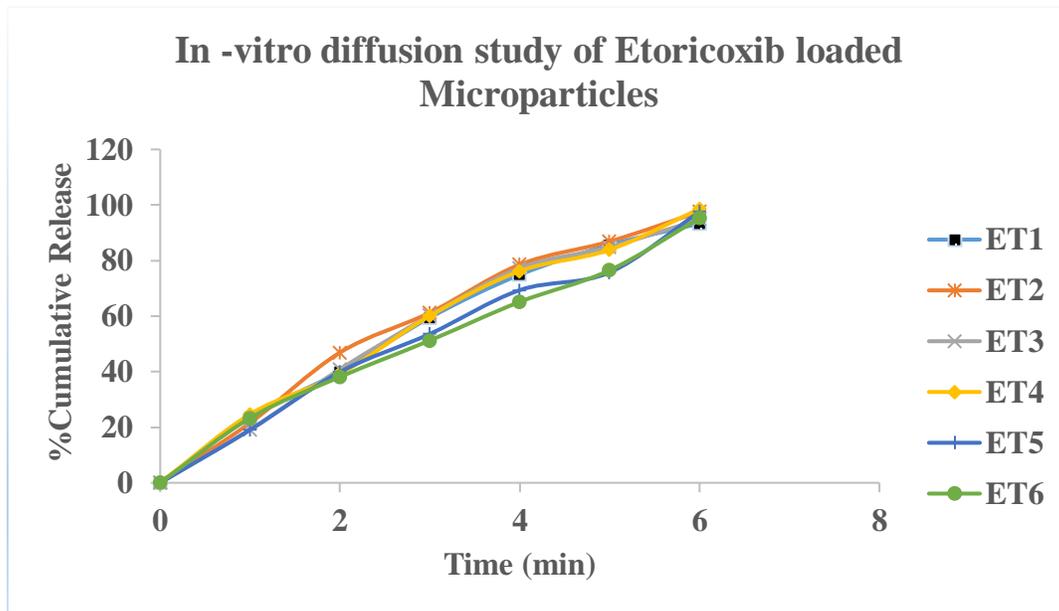


Fig 19. In -vitro diffusion study of Etoricoxib loaded Microparticle

#### Drug release kinetic study:

Kinetic models study is conducted to determine the release pattern of the drug from different dosage forms. By comparing the value of regression coefficient and  $n$  of all the kinetic equation, the best fit model and release mechanism for the formulations was determined. [13] Korsmeyer-peppas model is used to determine the release mechanism of the drug from the formulation. The  $n$ - value of Korsmeyer peppas ex ( $Mt/M = kt^n$ ) is used to predict the type of diffusion. The value of  $n$  is used to evaluate the type of diffusion, as  $n = 0.5$  means fickian diffusion,  $0.59$

means non-fickian diffusion and  $n=1$  means Anomalous diffusion is dependent on time. [14] On observing the  $n$ - value of Korsmeyer peppas equation ( $Mt/M = kt^n$ ) for all the formulations it was concluded that Anomalous transport is dominant which shows that the release of drug from dosage depends on the erosion of the carrier chain. In this type of diffusion the drug is surrounded by a polymeric membrane from which it is easily permeable. The core of the formulation acts as a reservoir for the drug. The drug first release to membrane from reservoir and then diffuses to systemic circulation.[15]

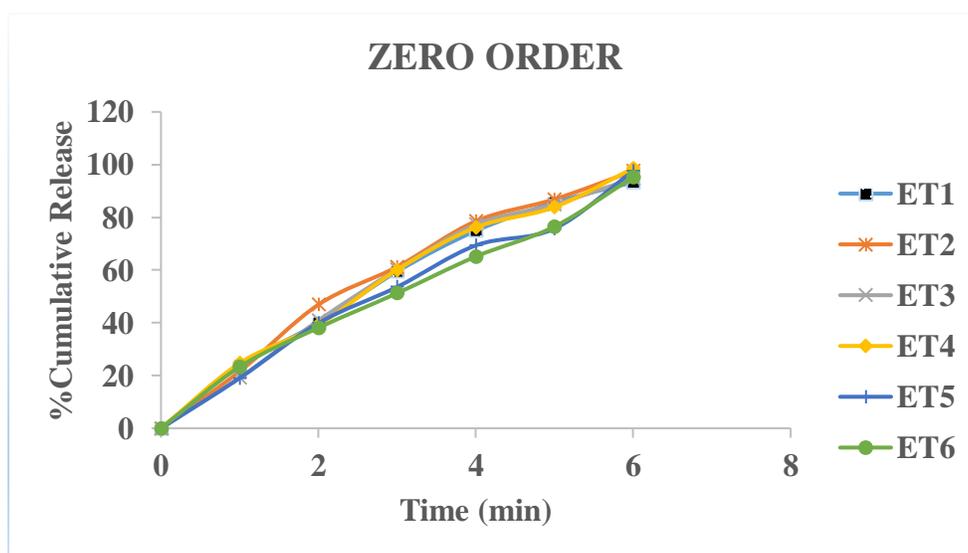


Fig 20. Drug release kinetic study in Zero order

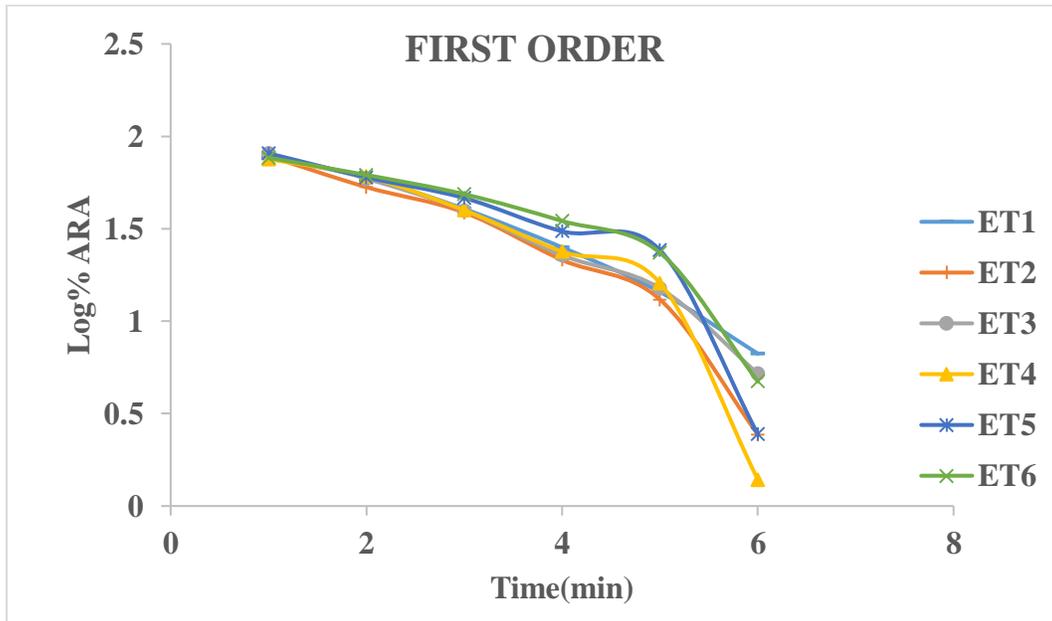


Fig 21. Drug release kinetic study in First order

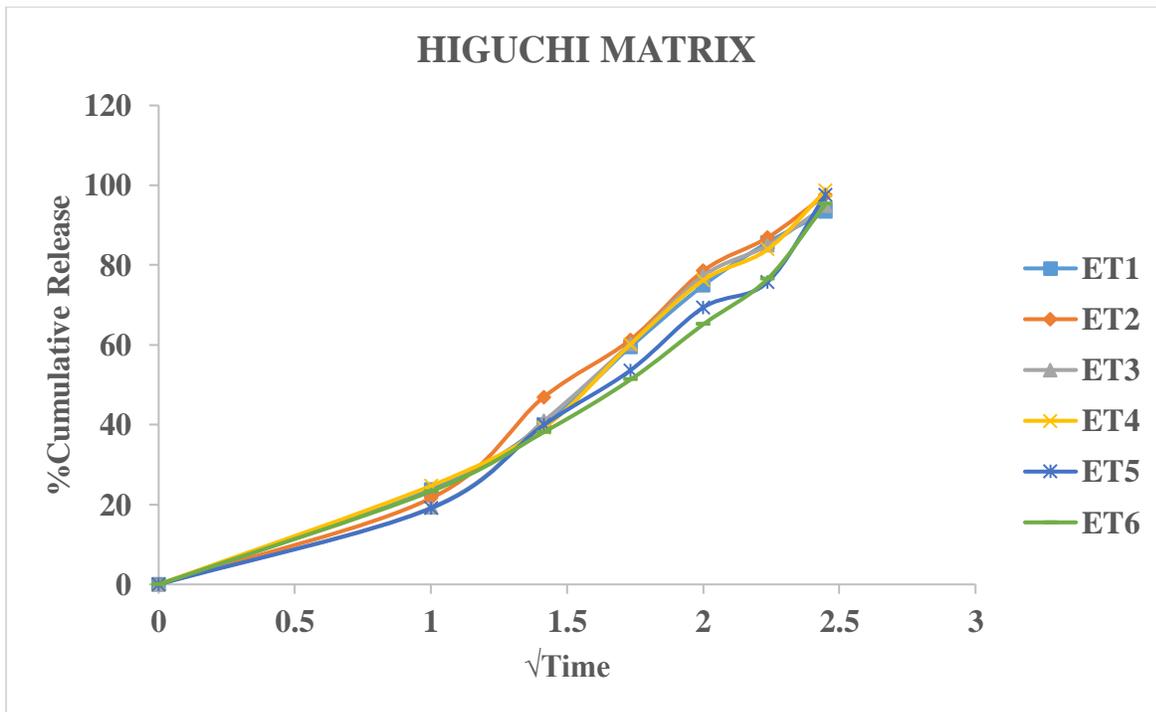


Fig 22. Drug release kinetic study in Higuchi matrix

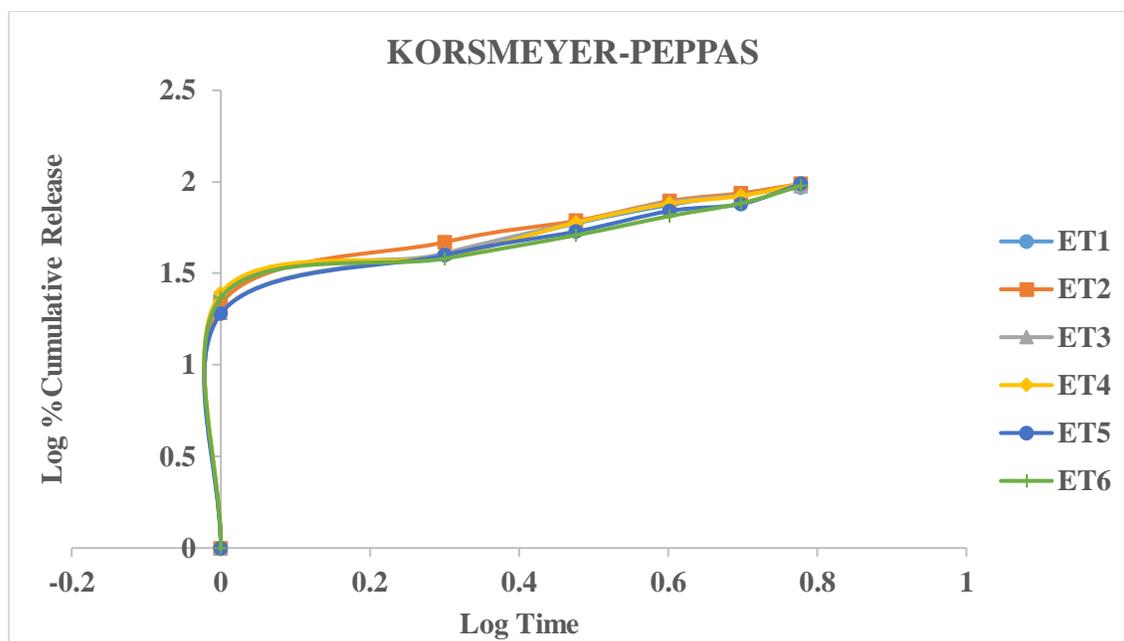


Fig 23. Drug release kinetic study in Korsmeier-peppas

Table no.8. In-vitro kinetic study of prepared formulation from ET1 to ET6

S.No.	Formulations	Zero order (R <sup>2</sup> )	First order (R <sup>2</sup> )	Higuchi matrix (R <sup>2</sup> )	Hixson Crowell (R <sup>2</sup> )	Korsmeier-peppas		Best fit model	Mechanism of release
						(R <sup>2</sup> )	n		
1	ET1	0.9760	0.9608	0.9196	0.9939	0.9941	0.7908	Korsmeier-peppas	Anomalous Transport
2	ET2	0.9700	0.8902	0.9243	0.9769	0.9803	0.8320	Korsmeier-peppas	Anomalous Transport
3	ET3	0.9738	0.9453	0.9245	0.9898	0.9835	0.8990	Korsmeier-peppas	Anomalous Transport
4	ET4	0.9821	0.8010	0.9165	0.9384	0.9928	0.7888	Korsmeier-peppas	Anomalous Transport
5	ET5	0.9863	0.7696	0.9145	0.9029	0.9900	0.8751	Korsmeier-peppas	Anomalous Transport
6	ET6	0.9906	0.8290	0.9082	0.9282	0.9282	0.7697	Korsmeier-peppas	Anomalous Transport

After comparing different evaluation parameters like percentage yield, particle size, zeta potential, PDI, percentage entrapment efficiency and in-vitro diffusion study ET4 was selected as the best optimized formulation. The particle size of the formulation ET4 was reported as 18.1 $\mu$ m, percentage yield as 57%, zeta potential as -18.2, PDI as 0.248. % entrapment efficiency as 99.36% and in-vitro diffusion as 98.41% in study period. Hence, it was concluded that formulation ET4 can be used for further study.

#### CONCLUSION:

The objective of the study was to formulate and evaluate solid lipid microparticles of Etoricoxib for

effective treatment of rheumatoid arthritis. In the present research, Etoricoxib loaded solid lipid microparticles were prepared by using modified solvent diffusion technique. For this, Graphene oxide is used as coating material with in conjugative bonding of  $\beta$ -cyclodextrin. Six formulations were prepared from which described in table. All these formulations further studied, After performing all the evaluation parameters, formulation ET4 was selected as optimized formulation because of its small particle size (18.2 $\mu$ m within 96.5% volume), mid ranged Polydispersity (PDI of 0.248), with zeta potential value -18.1 mV which lies in the range of zeta potential (- 25mV to +25mV) that is required for

effective delivery of drug loaded solid lipid micro formulation to intra-articular, low surface entrapment value (0.64 %), high drug entrapment (99.36 %) indicating higher amount of drug was entrapped in drug loaded Solid lipid Microparticle, 87.55 % drug release during 6min. study, Korsmeyer peppas release with Anomalous transport also known as Non fickian model indicating release of drug due to erosion of hydrophilic carrier.

From all the experimental studies, it may be concluded that the optimized formulation (formulation ET4) was able to cross the synovial barter and hence effectively reach to the target site (joints). So, it was confirmed that prepared formulation was able to provide better management of pain and hence improve patient compliance.

### REFERENCES:

- Suresh Bandi<sup>1,b</sup>, Vikram Hastak<sup>1,b</sup>, Chokkakula L.P. Pavithra, Sanjay Kashyap, Dhananjay Kumar Singh, Suaib Luqman, Dilip R. Peshwe, Ajeet K. Srivastav: Graphene/chitosan-functionalized iron oxide micro particles for biomedical applications. *Journal of Pharmaceutical Research*.2019;1-11
- Indian Pharmacopoeia 2010, Govt. of India, Ministry of Health and Family Welfare. Delhi: Indian Pharmacopoeial commission, Ghaziabad, 2010.
- Sarzi-Puttini P, Cimmino MA, Scarpa R, Caporali R, Parazzini F, Zaninelli A, Atzeni F, Canesi B. Osteoarthritis: An Overview of the Disease and Its Treatment Strategies. *Semin Arthritis Rheum*. 2005; 35:1-10.
- Hunter DJ, McDougall JJ, Keefe FJ. The Symptoms of Osteoarthritis and the Genesis of Pain. *Rheum Dis Clin N Am*.2008; 34: 623–643.
- Vonkeman HE, van de Laar MA. Nonsteroidal anti-inflammatory drugs: adverse effects and their prevention. *Semin Arthritis Rheum*. 2010; 39:294-312.
- Laine L, White WB, Rostom A, Hochberg M. COX-2 selective inhibitors in the treatment of osteoarthritis. *Semin Arthritis Rheum*. 2008; 38:165-87.
- Bingham CO, Bird SS, Smugar SS, Xu X, Tershakovec AM. Responder analysis and correlation of outcome measures: pooled results from two identical studies comparing etoricoxib, celecoxib, and placebo in osteoarthritis. *Osteoarthr. Cartil*. 2008; 16:1289-1293.
- Lin JH, Cocchetto DM, Duggan DE. Protein binding as a primary determinant of the clinical pharmacokinetic properties of non-steroidal anti-inflammatory drugs. *Clin.Pharmacokin*. 1987; 12:402-32.
- Gerwin N, Hops C, Lucke A. Intraarticular drug delivery in osteoarthritis. *Adv. Drug Deliv. Rev*. 2006; 58:226– 242.
- Larsen C, Ostergaard J, Larsen SW, Jensen H, Jacobsen S, Lindegaard C, Andersen PH. Intra-Articular depot formulation Principles: Role in the management of postoperative pain and arthritic disorders. *J.Pharm.Sci*. 2008; 97: 4622-4654.
- YannaZhao, YifeiGuo<sup>1</sup>, Ran Li, Ting Wang, Meihua Han, ChunyanZhu & XiangtaoWang: Etoricoxib Microparticles Prepared with Codendrimer from Polyamidoamine (PAMAM) and Oligoethylene Glycols (OEG)Dendron: Antitumor Efficacy in Vitro and in Vivo. *Scientific Reports*.2016;6:1-11.
- Deepak Kumar Gupta<sup>1</sup>, Rajveer Singh Rajaura and Kananbala Sharma: Synthesis and Characterization of Graphene Oxide Microparticles and their Antibacterial Activity. *Suresh Gyan Vihar University International Journal of Environment, Science and Technology*. 2015;1:16-24.
- Tian Yuan Z, Dan Qing C, Jian Qing G, Yu Lan H. Preparation of sertraline-loaded chitosan micro particles and the pharmacokinetics studies. *African Journal of Pharmacy and Pharmacology*. 2016; 10(3):26-33.
- Householder K, DiPerna D, Chung E, Wohlleb G, Dhruv H, Berens M et al. Intravenous delivery of Camptothecin-loaded PLGA micro particles for the treatment of intracranial glioma. *International Journal of Pharmaceutics*. 2015:479(2):374-380.
- Rodenak-Kladniew B, Islan G, de Bravo M, Durán N, Castro G. Design, characterization and in vitro evaluation of linalool-loaded solid lipid micro particles as potent tool in cancer therapy. *Colloids and Surfaces B: Bio interfaces*. 2017;154:123-132.