INTERNATIONAL JOURNAL OF PHARMACY AND ANALYTICAL RESEARCH

ISSN:2320-2831

IJPAR |Vol.8 | Issue 3 | Jul - Sep-2019
Journal Home page: www.ijpar.com

Research article *Open Access*

Formulation and evaluation of nanosuspension of etoricoxib for solubility enhancement

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ABSTRACT

The aim of the present study is to increase the solubility as well as dissolution rate of Etoricoxib drug by the preparation of nanosuspension of Etoricoxib by using different stabilizer namely Pvpk 30, Tween 80, PEG 6000, and PVA. This approach of delivering drug is mostly suitable for lipophilic drug and poorly or water insoluble drugs. Etoricoxib is a lipophilic drug that is practically insoluble in water and exhibit an excessively slow dissolution rate in class II compound in biopharmaceutics classification system Thenanosuspension of etoricoxib were prepared by High Pressure Homogenization (HPH) technique by using different concentration of stabilizers. The prepared Nano suspensions were evaluated for partical size, solubility studies, drug content, Dissolution study and Zeta potential studies. The saturated solubility studies and In-vitro dissolution studies as observes that the increase in solubility of drug and enhanced dissolution rate in nano suspension as compared to pure drug. The Formulation F2 and F8 is considered as best formulation as it has shown highest drug release in short time. Our studies showed that the solubility of the drug can be significantly enhanced with increase in the stabilizers concentration there is increase in the solubility resulting in enhanced dissolution rate.

Keywords: Nanosuspension technology, Etoricoxib, Stabilizers, High Pressure Homogenization. Solubility enhancement.

INTRODUCTION

Solubility is an important factor that govern the absorption of orally administered drug. It is estimated that upto 50% of orally administered drug having poor hydrophilicity. Different techniques are employed to enhance the dissolution of poorly soluble drugs like use of water soluble salt and polymorphic forms, solid dispersion, reducing particle size to increase the surface area, pH adjustment, co-precipitation, polymer modification Lyophillization, microencapsulation and nanosuspension technique. Nanosuspension technique is an attractive and promising alternative to improves drug dissolution rate and efficacy of poorly soluble or water insoluble drugs.

Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10^{-9} m. Nanosuspension are submicron colloidal dispersions of nanosized drug particals stabilized by surfactants [1].

Etoricoxib (5-chloro-2-[6-methyl pyridine-3-yl]-3-[4-methylsulfonylphenyl] pyridine) is a novel, selective second-generation cyclooxygenase-2 inhibitor administered orally as an analgesic and anti-inflammatory drug. Etoricoxib does not inhibit prostaglandin synthesis in the gastric mucosa, even at doses above the clinical dose range of 60-120 mg [2, 3].

The main objective of the study is to investigate the possibility of improving the solubility and dissolution rate of Etoricoxib by formulating nanosuspensions by High Pressure Homogenization (HPH) technique using different concentration of stabilizers namely pvpk 30, Tween 80, PEG 6000, and PVA. The drug release profile of formulated nanosuspensions were compared with that of pure drug [4].

MATERIALS AND METHOD

MATERIALS

Etoricoxib was received as a gift sample from Glenmark pharmaceuticals limited (pithampur).Polyethylene glycol (PEG 6000) was procured from central drug house (P) LTD (New Delhi). PVPK30 from HiMedia Laboratory Pvt Ltd (Mumbai). Tween 80 from Qualichems (vadodara). PVA from Sd Fine- chem. limited (Mumbai). All other solvent and reagent are used was of analytical grade.

EXPERIEMENTALS

Identification of drug

By UV Spectroscopy

In order to ascertain the optimum wavelengths of Etoricoxib, the solution of Etoricoxib in phosphate buffer was scanned on UV-Visible Spectroscopy in the range of 200-400 nm against phosphate buffer 7.4 as blank [5]. spectrum of etoricoxib is shown in fig. 1.

By melting point determination

Melting point determination of drug was performed using melting point apparatus (BTI-34) Melting point apparatus, Mumbai, India). In this method small amount of drug was filled in capillary tube open from both ends and it was placed along with thermometer in melting point apparatus. The temperature in the heating stand is ramped at user programmable fixed rate until the sample in the tube transition into the liquid state [6].Melting point of drug sample is shown in table 1.

By Fourier transform infrared spectroscopy analysis

Identification of Etoricoxib was done by FTIR Spectroscopy. The sample was analysed by FTIR instrument (IR Affinity-1,(Shimadzu, Japan) was scanned and recorded. [7] The obtained IR spectrum is shown in fig .2

Preparation of standard Calibration curve of Etoricoxib

Standard stock solution of Etoricoxib was prepared by dissolving 100 mg of drug in 100 ml of phosphate buffer 7.4 (1000 µg/ml) from the above stock solution 10 ml was taken and diluted to 100 ml in phosphate buffer 7.4 (100 µg/ml). From the above solution 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0 ml was taken and diluted upto 10 ml with phosphate buffer 7.4 to get series of solutions in concentration. Absorbance was noted using UV-VIS Spectrophotometer at 288 nm against blank (phosphate buffer 7.4) [8]. The calibration curves of etoricoxib are shown in the fig.3.

Solubility study

Solubility of Etoricoxib was determined in distilled water and various non aqueous solvents like PEG 400, methanol, ethanol, HCl, chloroform, phosphate buffer 7.4. Excess amount of Etoricoxib was saturated in 10 ml of selected solvents in conical flask for determination of solute dissolved in each solvent and was shaken at 25^{o}C for 24 hrs. After 24 hrs equilibrium would be attained and the sample was filtered through whatman filter paper. the samples was analysed after suitable dilution for the concentration of drug dissolved using UV-VIS Spectrophotometer.[9] The solubility of etoricoxib in different solvents are shown in table 2.

Method of preparation of nanosuspension

Nanosuspension of etoricoxib were prepared by High Pressure Homogenization technique by using different concentration of stabilizers namely as PVA, PEG 6000, Tween 80, and PVPK30.

Respectively, The accurately weighed quantity of drug Etoricoxib (50 mg) and different concentrations of stabilizers were mixed in water by mechanical stirring for 15 min. Then this suspensions are subjected to high pressure homogenizer for 10 min. Later suspensions were loaded in high pressure homogenization on different pressure like 600, 800, 1000, bar and 3,5,7,10,15,20,30 cycles are requied [9].

Various pre- treatment process and formulation parameters like homogenization pressure, homogenization cycles, type of stabilizer, and concentrations were optimized in order to get desire results.

Screening of Stabilizers

In order to screen stabilizer total twelve batches (B1 to B12) of etoricoxibnanosuspensions were prepared by using 4 different type of stabilizers at different concentration as shown in table 1 by High Pressure Homogenization technique at 1000 bar pressure and 30 cycles which are kept constant in all the batches. Sce=reening was done on the basis of their appearance and liquid state stability [9].

Table 3: Screening of stablilizers

Batches	Stabilizers	Drug and Stabilizer ratio
B1	PVA	1:1
B2	PVA	1:2
B3	PVA	1:3
B4	PEG6000	1:1
B5	PEG6000	1:2
B6	PEG6000	1;3
B7	PVPK 30	1:1
B8	PVPK 30	1:2
B9	PVPK 30	1:3
B10	Tween 80	1:1
B11	Tween 80	1:2
B12	Tween 80	1:3

Optimization of formulation

To optimize the stabilizers and its concentration, total 8 batches (F1 to F8) were prepared using different concentration of drug and stabilizers are shown in table 2. All the batches are evaluated for particle size, drug content, saturation solubility, In vitro drug release and zeta potential studies.

Table 4: Optimization of drug to stabilizers ratio

Batches	Stabilizers	Drug and Stabilizer ratio
B1	PVA	1:1
B2	PVA	1:2
B3	PEG6000	1:1
B4	PEG6000	1;2
B5	PVPK 30	1:1
B6	PVPK 30	1:2
B7	Tween 80	1:1
B8	Tween 80	1:2

EVALUATION OF PREPARED NANOSUSPENSION

Particle Size determination

Mean particle size and size distribution analysis was carried out by using Malvern zeta sizer Nano-S90.Which follows principle of LAZER light differaction or also called photon correlation spectroscopy(pcs). It is based on measurement of Brownian motion of particles [9]. The particle size of F2 and F8 batches are shown in the fig.4, 5.

Determination of saturation solubility

Solubility study was performed according to method reported by Higuchi and Connors. The formulated nanosuspensions batches F1,F2,F3,F4,F5,F6,F7 and F8 were added in 10 ml distilled water taken in stoppered conical flask and were shaken for 24 hrs at 37^0C±1 in orbital shaker. Two ml aliquots were withdrawn at 1 hr intervals and filtered through whatman filter paper. The filtered solution were analysed spectrophotometrically at 288 nm against blank [10].The saturated solubility of nanosuspensionsare shown in fig 6.

Determination of drug content in formulations

The nanosuspension equivalent to unit dose of drug was weighed accurately and dissolved in 100 ml of phosphate buffer 7.4 and. The solutions were filtered Throughwhatman filter paper and analysed by UV spectrophotometer at 288 nm [11]. The drug content calculated accordingly. Drug content of various formulations are shown in table 6.

In vitro Drug Release Studies

In vitro drug release of nanosuspensions was determined by using a dialysis tube(doner compartment) containing the known sample of quantity (10 ml) of nanosuspension in a water-jacketed beaker containg 300 ml of phosphate buffer pH 7.4 at 37^0 C for 1 hr. The sample were withdrawn 5ml for 5,10,15,30, 45, 60 min. and replaced with 5 ml volume of fresh phosphate buffer 7.4. The sample was filtered through whattman filter paper and assayed by measuring the absorbance at 288 nm using the UV-visible spectrophotometer[12]. The drug release profile of various formulations are shown in fig. 7,8,9,10.

Zeta potential

The zeta potential of all the batches was measured using zetasizer Nanoseries Nano-ZS (Malvern instrument, The sample was diluted 100 times with distilled water[13]. The zeta potential of F2 and F5 batches are shown in fig.11,12

RESULT AND DISCUSSION

UV Spectroscopy

The λ max was found at 288 which shows that drug is pure. As given in the reference.

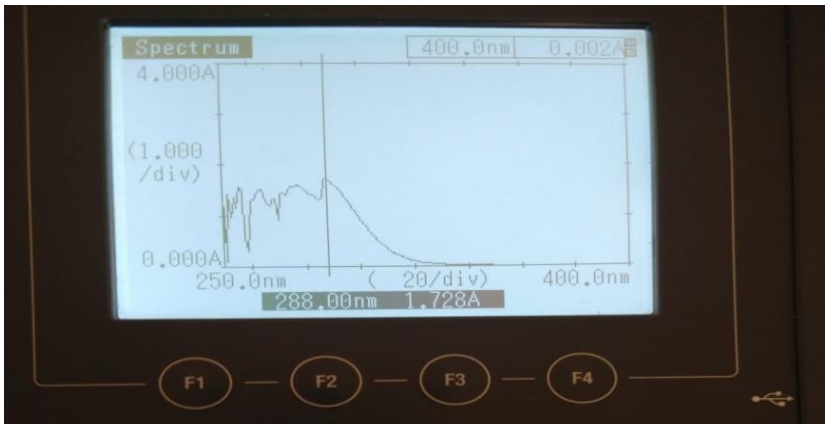

Figure- 1.Lamda max of etoricoxib

Melting point

The melting point of drug sample was determined by using melting point apparatus. The melting point was found between the range of 135 -136^{0}C. As given in the refrence. The melting point of pure drug is shown in table 1.

Table 1: Melting Point of Etoricoxib

Drug	Observed	Refrence
Etoricoxib	135-136^{0}C	134^0-138^{0}C

Fourier transform infrared(FTIR) spectroscopy

The IR spectra of Etoricoxib are given in the figures. The spectrum of pure Etoricoxib presented characteristic signals at 1600.1, 1402.2, 1400.3, 1400,1300, 1090.5, 100.2, 900, 889.2, 800.1, 750.1, 655.2, 600, 595.2, 545.2, 400cm^{-1}. This shows that drug is pure. The IR Spectra of drug is shown in fig.2

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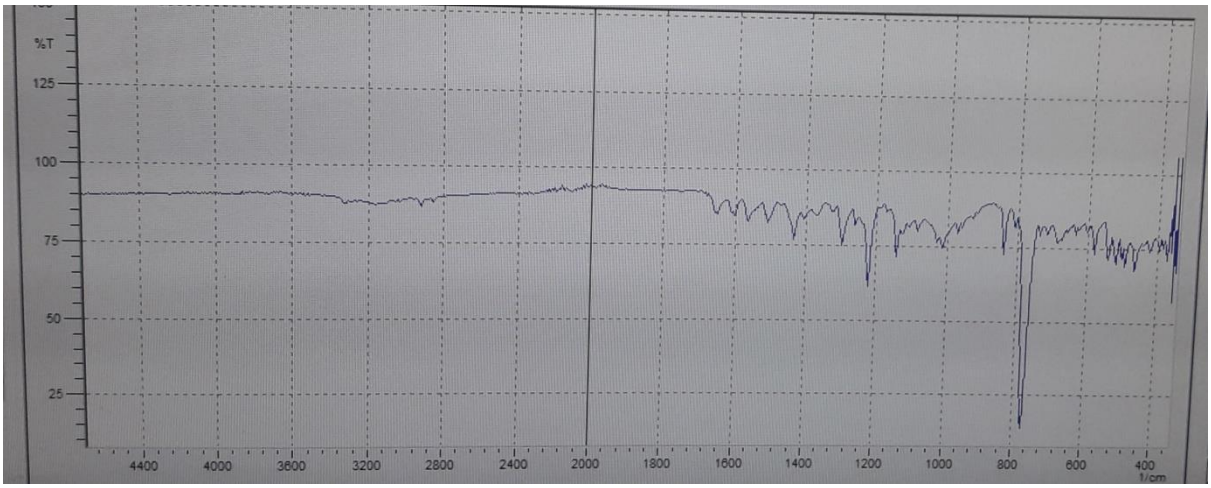

Fig.2: FTIR of pure drug (Etoricoxib)

Solubilty studies

Quantitative solubility analysis of etoricoxib determined in different solvents and the results were illustrated in table. The etoricoxib drug was found to be more soluble in ethanol, phosphate buffer and PEG 400. The solubility of etoricoxib in various solvents are shown in table 2.

Table 2: solubility of etoricoxib in various solvents

S.No	Solvents	Solubility mg/ml
1.	Water	0.033
2.	Ethanol	0.134
3.	Phosphate buffer 7.4	0.121
4.	HCl	0.110
5.	PEG 6000	0.156
6.	Chloroform	0.120

Standard curve of etoricoxib

The UV spectrum of the drug in the range of 200-400 nm on UV visible spectrophotometer revealed that wavelength of maximum absorption of etoricoxib was 288 nm. From the graph of absorbance vs. Concentration for pure etoricoxib it was observed that the drug obeys beer's law in concentration range of 5 to 5o µg/ml (R^2=0.999) at 288 nm.(Fig.3)

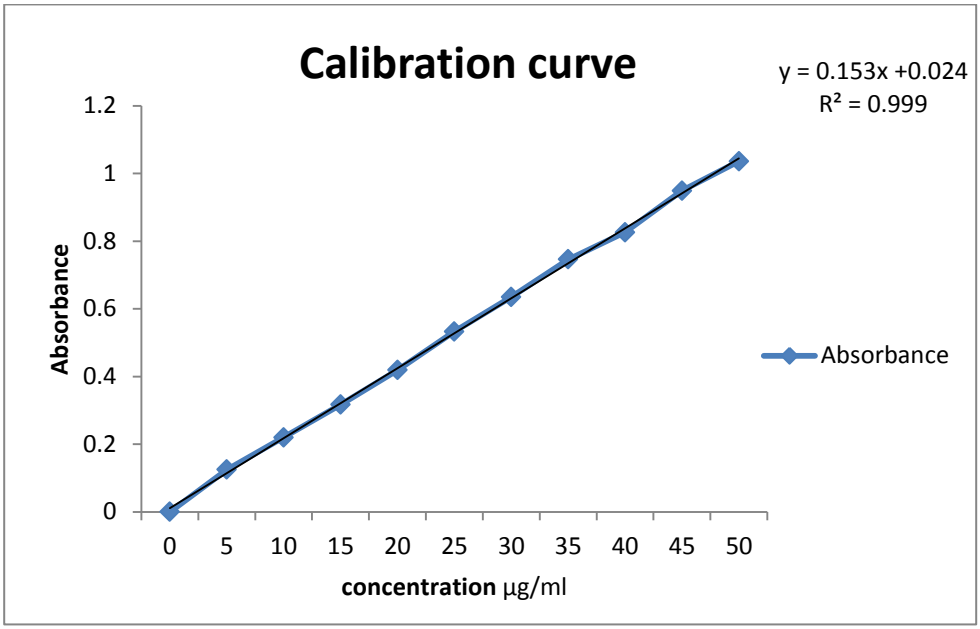

Fig.3.Calibration curve of Etoricoxib in phosphate buffer 7.4.

Particle Size

Partical size determination is the most important evaluation test to check the dispersibility and homogenieity of nanosuspension. The batch F2 and F8 had partical size 241.2 and 489.1. Therefore can be considered as physically stable nanosuspension. The particle size of F2 and F8 batches are shown in fig.4, 5.

Particle size of F2 Batch

Z-Average (r.nm):	241.2	**Peak 1: Peak 2: Peak 3:**	**Size (r.nm):**	**% Number**	**Width (r.nm):**
PdI: Intercept:	1.000		0.6645	100.0	0.09875
	1.25		0.000	0.0	0.000
			0.000	0.0	0.000

Result quality: GOOD

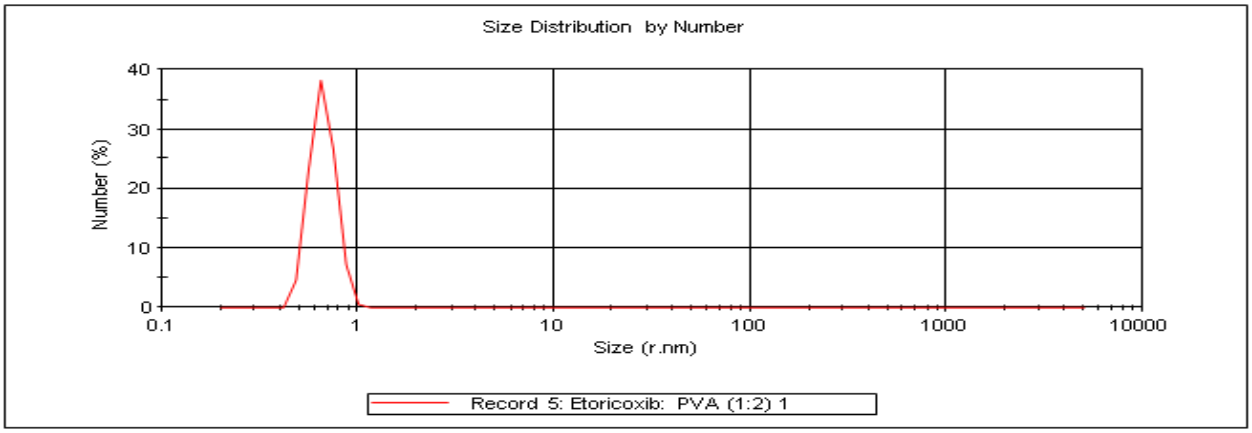

Fig 4: particle size of F2 batch

Partical Size of F8 Batch

Z-Average (r.nm): 589.6	**PdI: 0.014**	**Intercept: 0.965**	**Peak 1: Peak 2: Peak 3:**	**Size (r.nm): % Volume Width (r.nm):**
			498.9 100.0 89.18	
			0.000 0.0 0.000	
			0.000 0.0 0.000	

Result quality : Good

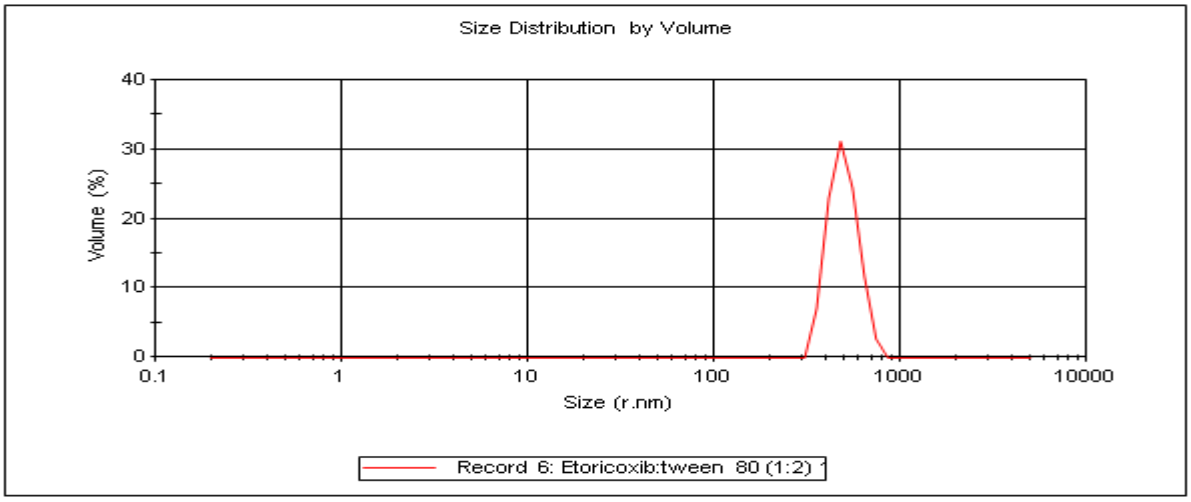

Fig.5: Particle size of F8 batch

Determination of saturation solubility

Saturation solubility studies were carried out for pure drug, as well as for prepared nanosuspension. From the result of saturation solubility studies it was observed that there was increase in solubility of drug in nanosuspension as compared to pure drug. With increase in the concentration of stablizers increased and the nanosuspension containing PVA and Tween 80 in (F2) and (F8) has increased the solubility up to five times. Which is improves its wettability resulting in a significant increase in solubility. The saturation solubility of various formulations are shown in fig 6.

Table.4: Saturation solubility study of various formulation:

S.NO	Formulation Code	Saturation Solubility (µg/ml) at 37^0 C in water	Percentage Solubility Enhancement%
1	Pure Etoricoxib	0.0035	-
2	F1	0.0084	24%
3	F2	0.0102	29%
4	F3	0.0082	23%
5	F4	0.0074	21%
6	F5	0.0063	18s%
7	F6	0.0089	25%
8	F7	0.0094	26%
9	F8	0.013	32%

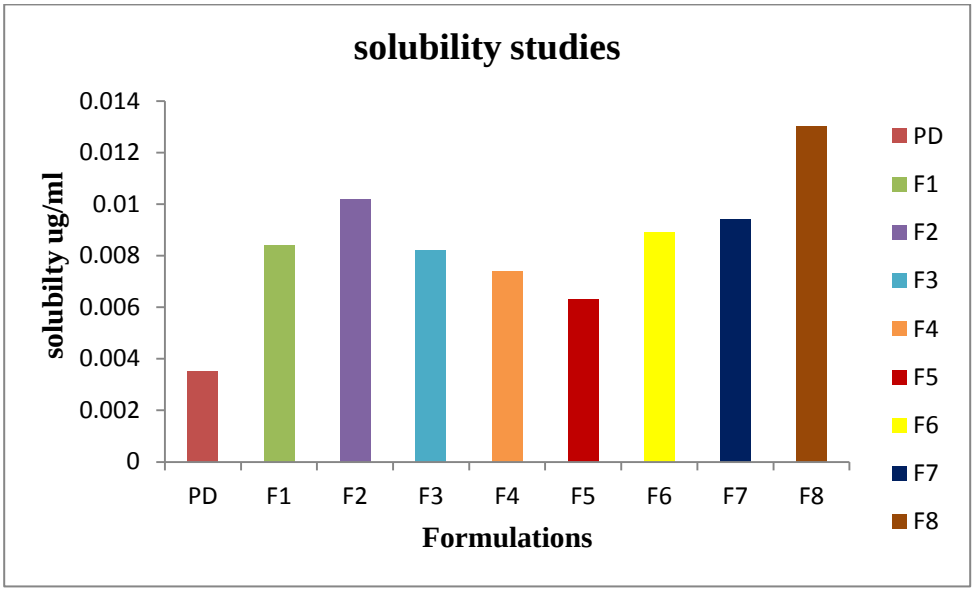

Fig.6: Solubility graph of batches F1 to F8

Drug content

The drug content estimation was done to ensure uniform distribution of drug. The drug content of Nanosuspensions of etoricoxib was performed for all the prepared formulations. The result indicates that in all the formulations drug content was uniform between 88% to 97% which was analysized spectrophotometrically atλmax 288nm. The drug content of various formulations are shown in table 5.

Table.5: Drug content of various formulation.

S.NO	Formulation Code	% Drug content
1.	F1	88%
2.	F2	96%
3.	F3	88%
4.	F4	94%
5.	F5	96%
6.	F6	92%
7.	F7	88%
8..	F8	97%

In-vitro drug release studies

The in vitro drug profiles of pure drug Etoricoxib, nanosuspensions in dissolution medium are shown in figure (7,8,9,10). The formulated nanosuspensions of Etoricoxib showed a significant increase in the dissolution rate as compared with pure Etoricoxib. In the nanosuspension's formulations F1 and F2 showing 90.9% and 95.2% drug relase, F3 and F4 showing 86.6%and 91.2% drug release, F5 and F6 showing 91.2% and 93.3% and F7 and F8 showing 86.6% and 97.2 % drug release respectively. All the formulation showed improves drug release rate as compared to pure Etoricoxib.

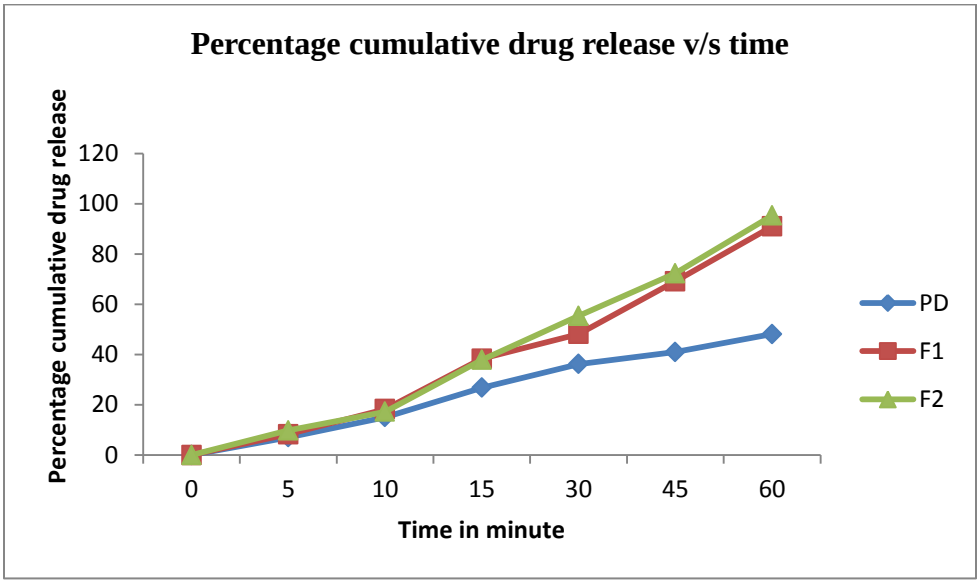

Fig.7:Comparison of In- vitro release of pure Etoricoxib& F1,F2 Batches.

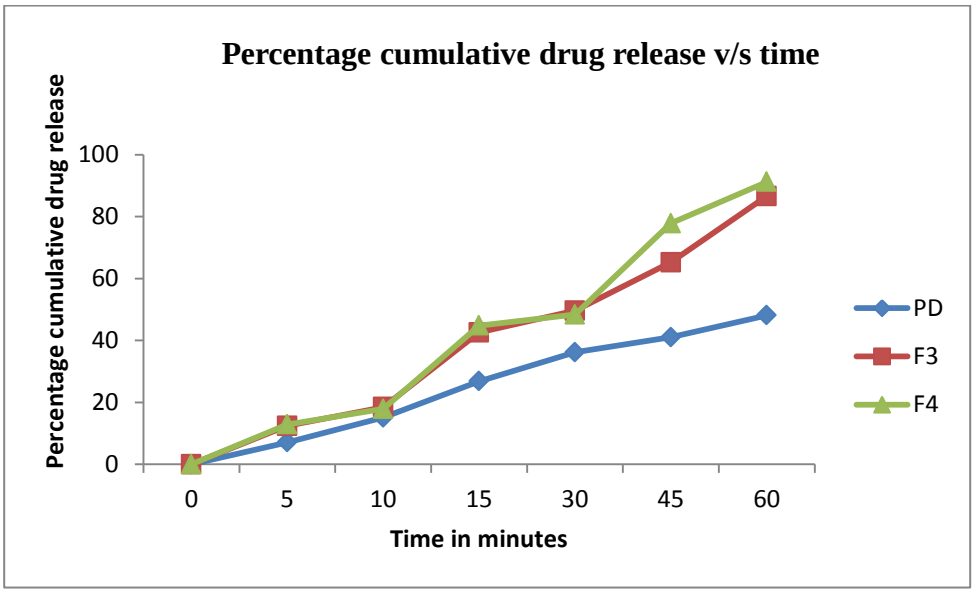

Fig.8: Comparison of In- vitro release of pure Etoricoxib& F3,F4 Batches

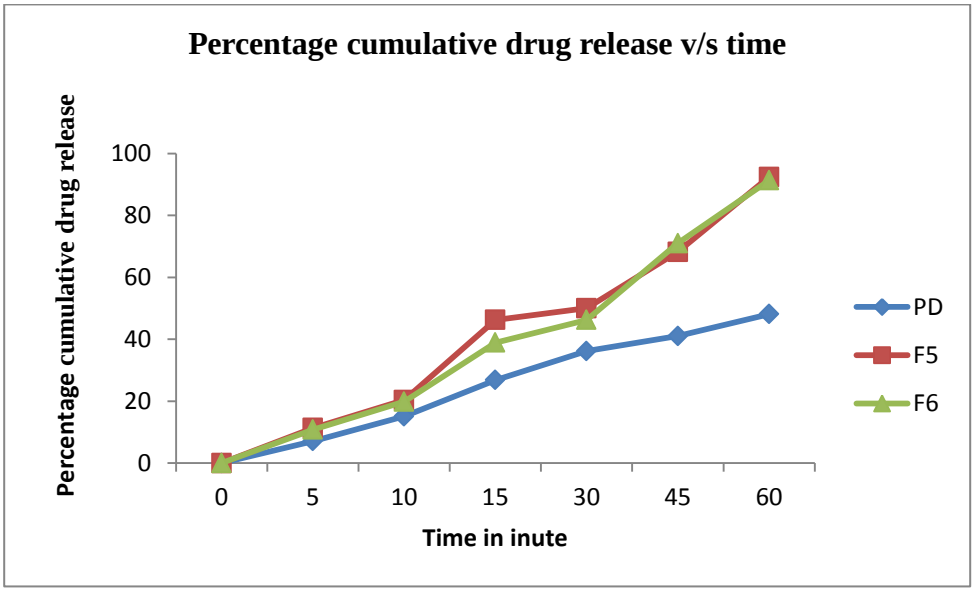

Fig.9:Comparison of dissolution profile of pure Etoricoxib& F5,F6 Batches

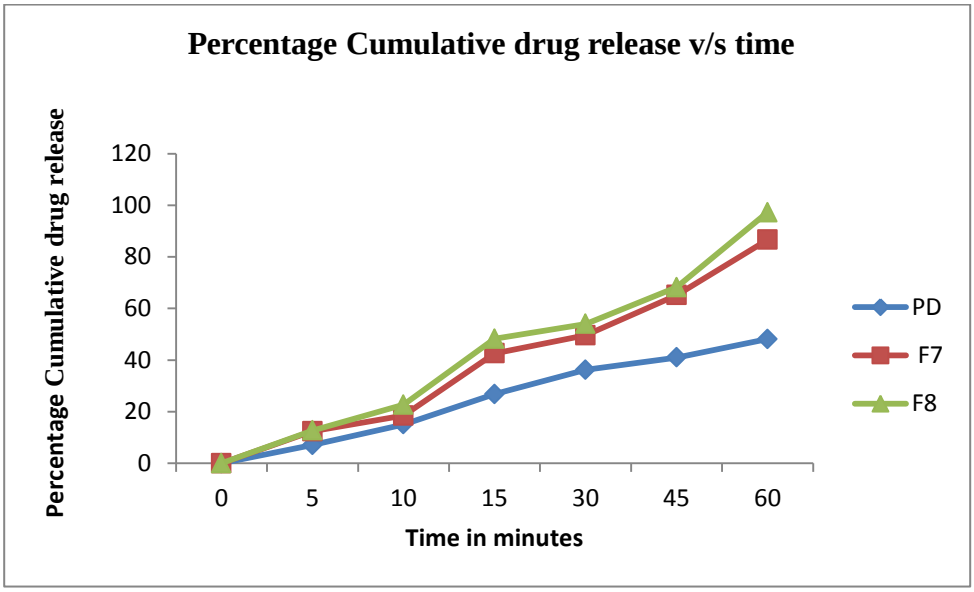

Fig.10:Comparison of dissolution profile of pure Etoricoxib & F7,F8 Batches

Zeta potential

The zeta potential of optimized formulation batch F2 and F8 was found to be -11.56 and -10.18 indicating good stablilty of formulation. The zeta potential of F2 and F8 are shown in fig.11,12.

Zeta potential of F2 Batch

			Mean (mV)	Area (%)
Zeta Potential (mV):	-11.56	**Peak 1:**	-11.56	100.0
Zeta Deviation (mV):	3.19	**Peak 2:**	0.00	0.0
Conductivity (mS/cm):	0.165	**Peak 3:**	0.00	0.0

Result quality: Good

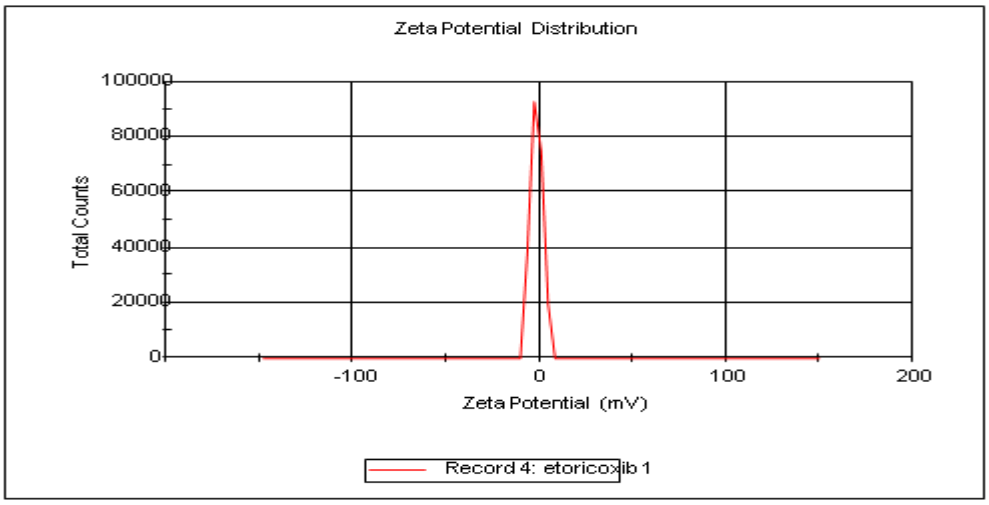

Fig.11. Zeta potential of F2 Batch

Zeta potential of F8 Batch

Zeta Potential (mV): Zeta Deviation (mV):			**Mean (mV)**	**Area (%)**
Conductivity (mS/cm):	-10.187	**Peak 1:**	-10.187	100.0
	4.53	**Peak 2:**	0.00	0.0
	0.246	**Peak 3:**	0.00	0.0

Result quality :Good

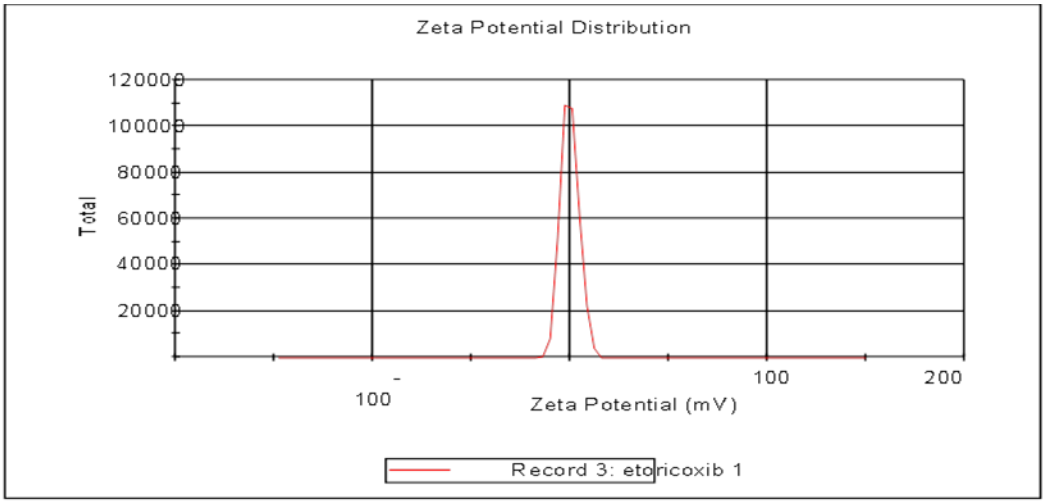

Fig. 12: Zeta potential of F8 Batch

Acknowledgement

The author would like to thank to the management of Swami Vivekananda college of pharmacy Indore. For providing necessary facilities for conducting the research work and heartily thankful to my guide for providing all the support and encouragement to carry out this studies.

CONCLUSION

The observations showed that there was a poor drug release rate in case of conventional formulation. Improvement of aqueous solubility in such case is valuable goal to improve therapeutic efficiency. Thus nanosuspension containing etoricoxib and PVA (1:2) and nanosuspension and

tween 80(1:2) showed better enhancement in drug release rate and solubility of drug.

From the in vitro drug release studies the optimized formulation F2 and F8 showed fast drug release when compared to pure drug. The formulation F2 and F8 showing 95.2 and 97.2 % drug release. In conclusion, the nanosuspension can be promising alternative for the formulation of water – insoluble drugs.

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