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Formulation and Development of Capsule in Capsule Drug Delivery System for Biphasic Delivery of Etoricoxib

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Keywords: Biphasic drug delivery system, Capsule-in-a-capsule formulation, Fast releasing liquid-filled-capsules, Slow release beads-filled-capsules

ABSTRACT

In the present research work, a novel capsule-in-a-capsule technology for biphasic delivery of Etoricoxib was developed for the treatment of arthritis. The advantages of fast releasing liquid-filled-capsules and slow release beads-filled-capsules were combined to meet the optimized requirements of biphasic drug delivery system. Etoricoxib slow releasing beads were prepared by ionotropic gelatine method by using hydrophilic polymers and were filled into a smaller capsule. Etoricoxib fast releasing liquid dispersion was prepared by using crospovidone and croscarmellose sodium carriers and further dissolving in starch solution. This fast releasing liquid and slow releasing beads-filled-capsule was further inserted into a bigger capsule body and closed with the cap by sealing. The various formulation batches were subjected to physicochemical studies, entrapment efficiency, drug content, *in vitro* drug release and stability studies. Interaction studies reveal that there was no interaction between drug and polymers employed in this study. The optimized capsule-in-a-capsule formulation released 94.31% of drug at the end of 30 min and 98.66% of drug at the end of 12hr. The drug release profile of etoricoxib capsule-in-a-capsule formulation fits well with model of First order followed by zero order, Higuchi model and Korsmeyer-Peppa's model. Korsmeyer-Peppas model analysis indicated that the drug release followed non-Fickian transport mechanism. The stability results indicated that the various parameters of optimized formulation are not affected on storage at 45°C/75%RH up to 3 months.

INTRODUCTION[1,2]

Biphasic drug delivery systems are designed to release a drug at two different rates or in two different periods of time. i.e. they are either quick/slow or slow/quick . In the first phase of drug release, the immediate release dose fraction (also called "loading-dose") reaches a therapeutic drug level in the blood plasma quickly after administration, which is responsible for quicker onset of action. The second phase consists of extended release dose fraction (called the "maintenance dose"), which maintains an effective therapeutic level for a prolonged period. Examples of such biphasic drug delivery systems are bilayer tablets, drug layered matrices, or combinations of immediate, and extended release multi particulates .

The word Capsule is derived from latin word "capsula" which means a small box or container. In pharmacy, capsule word has been used as describe a glass ampules and also name of protective cap over the stopper of a bottle of medicine. In more recent times, capsule has been used primarily to described solid dosage forms, which consist of container, filled with medicinal substance. They can be divided into main two categories, hard capsule(two pieces) and small capsule(one piece) according to presence of glycerol or another plasticiser which make it soft and elastic. Capsule in a capsule formulation consist of two phases; immediate and sustained releasing phases.

Etoricoxib[3]:-

Fig no 1 :-Chemical structure of Etoricoxib

Etoricoxib is one of the group of medicine called selective COX 2 inhibitors. These belong to family of medicines called non- steroidal anti-inflammatory drugs (NSAIDs) of the oxicam class with analgesic, anti-inflammatory and antipyretic properties. It is used as Rheumatoid arthritis**,** Osteoarthritis, Gout, chronic low back pain, acute pain and gout.

MATERIALS AND METHODS

Material:-

Etoricoxib was obtained as a gift sample from Torrent Research Center, Ahmedabad. Crospovidone, Sodium alginate and Calcium chloride from SD fine chemical limited Mumbai. Starch and acetic acid from LOBA Chemic Pvt. Ltd., Mumbai. Potassium bicarbonate and Guar gum from Milton Chemicals, Mumbai.

Method:-

1. Preparation of immediate release phase[4,5]-

Accurately weighed amounts of Crospovidone were placed in an aluminum pan on water bath and melted, with constant stirring with a glass agitator, at 60°C.Fusion was reached in 20min at this temperature. Accurately weighed amount of Etoricoxib was incorporated into the melted carrier with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. The drug:carrier complex melt of Etoricoxib was solubilized in starch solution to give a final drug concentration of 3% (m/m) and further sonicated for 1hr.

Table no 1:- Composition of Immediate release capsules

Formulation code	Drug (mg)	Crosspovidone (mg)	Croscarmellose sodium(mg)	Starch(mg)
F1	60	30	-	25
F2	60	35	-	25
F3	60	40	-	25
F4	60	-	30	25
F5	60	-	35	25

2. Preparation of sustained release phase[6,7]:-

Accurately weighed amount of sodium alginate and guar gum was dissolved in deionized water, accurately weight of Etoricoxib and various amount of potassium bicarbonate were uniformly mixed. The dispersion was sonicated for 30 min to remove any air bubbles.The resultant dispersion was dropped via 18 gauge syringe needle into calcium chloride solution

containing acetic acid. The content was stirred at 100rpm using magnetic stirrer for 15 min. The beads were then filtered, washed three times with distilled water and subsequently oven dried at 50^0C for 4hr.

Table no. 2:- Composition of Sustained release capsules

Formulation code	Drug (mg)	Sodium alginate (mg)	Calcium chloride (2%w/w) (gm)	HPMC (mg)	Potassium bicarbonate (mg)	Sodium bicarbonate (mg)	Guar gum (mg)
F1	60	30	2	-	4	-	25
F2	60	30	2	-	8	-	25
F3	60	30	2	4	-	-	25
F4	60	30	2	8	-	-	25
F5	60	30	2	-	-	4	25

3. Preparation of capsule-in-a-capsule:-

Special leak proof capsules for both smaller and bigger size was used in this formulation. To prepare a novel capsule in- a-capsule technology the prepared optimized sustained release beads of Etoricoxib were filled in size ‘2’ hard gelatin capsule and was sealed with 15% (*m/m*) warm gelatin solution. This prepared sustained release smaller capsule was filled into a bigger capsule body size ‘0’ which was further filled with the liquid dispersion of Etoricoxib as loading dose using medicine droppers. After closing with cap the bigger capsule was also sealed with 15% (m/m) warm gelatin solution. The filled capsules were stored at room temperature until testing.

RESULTS AND DISCUSSION

1. Calibration curve of Etoricoxib: -

The calibration curve of Etoricoxib were obtained in following solvents:

HCl (0.1N): 10 mg of Etoricoxib was dissolved in 100 ml 0.1N HCl and subsequently diluted 5 times using 0.1N HCl. This solution was further diluted with 0.1N HCl to produce 5-25 µg/ml of Etoricoxib. Absorbances of these solutions were noted using UV/VIS spectrophotometer (Jasco V-530, Japan) at the maximum wavelength (nm) of drug using 0.1 N HCl as blank.

Phosphate buffer (pH-6.8):10 mg of Etoricoxib was dissolved in 100 ml phosphate buffer (pH-6.8) and subsequently diluted 5 times using phosphate buffer (pH-6.8). This solution was further diluted with phosphate buffer (pH-6.8)to produce 5-25 µg/ml of Etoricoxib. Absorbance of these solutions were noted using UV/VIS spectrophotometer (Jasco V-530, Japan) at the maximum wavelength (nm) of drug using phosphate buffer (pH-6.8) as blank.

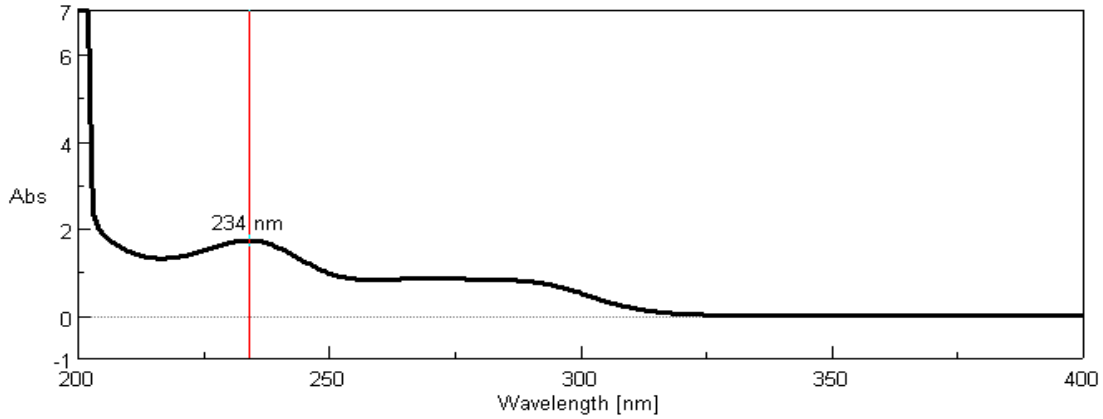

Fig no 2. UV Spectra of Etoricoxib in 0.1 N HCl

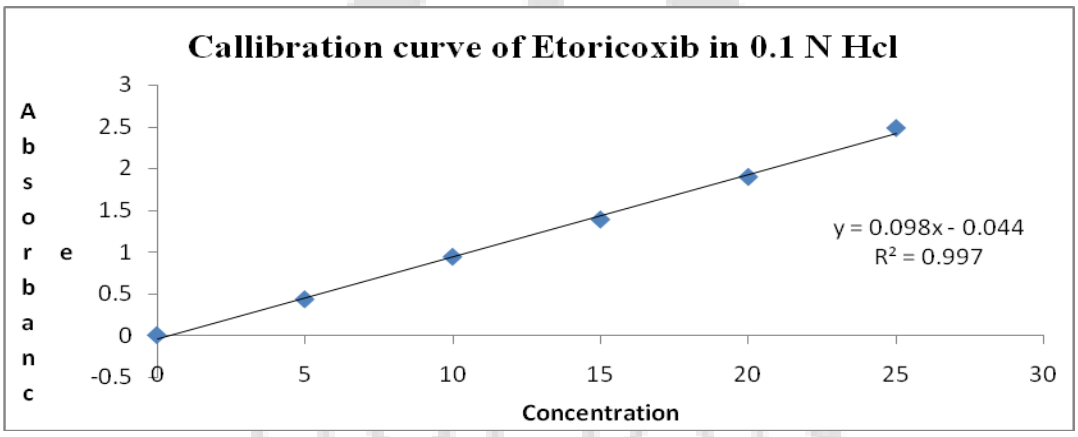

Fig no 3. Calibration curve of Etoricoxib in 0.1 N HCl

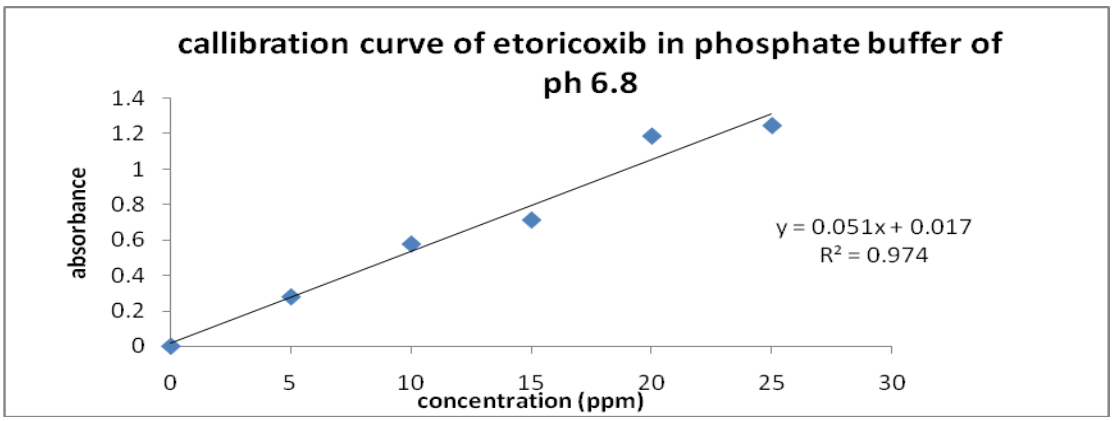

Fig no 4. Callibration curve of etoricoxib in phosphate buffer of ph6.8

Table no 3. Results of Angle of repose, Drug content and Entrapment efficiency

Batches	Angle of repose	Drug content (%)	Drug entrapment efficiency (%)
LFC-1	-	95.58%	-
LFC-2	-	95.15%	-
LFC-3	-	96.37%	-
BFC-1	25.14°	93.22%	86.60%
BFC-2	29.45°	96.45%	90.80%
BFC-3	27.56°	96.43%	79.2%
BFC-4	19.78°	95.41%	83.66%
BFC-5	23.24°	94.22%	81.71%

The angle of repose of different batches were found to be in the range of 19.78°to 29.45° which indicates good flow properties of the beads. The mean drug content of liquid dispersion and beads was studied and the values were found to be more than 95%, and maximum drug content of beads was LFC-3(96.37%) and BFC-2 (96.45%). The drug entrapment efficiency of the sustained release beads was also studied and the values were found to in the range between 79.2% to 90.8% and the maximum drug entrapment was found to be in BFC-2 batch i.e. 90.80 as shown in Table 3.

***In vitro* drug release studies:-**

Table no 4. *In vitro* % drug release in 0.1N HCl

Time in min	*In vitro* % drug release				
	F1	F2	F3	F4	F5
0	0.000	0.000	0.000	0.000	0.000
5	15.670	19.502	20.300	10.239	12.786
10	36.289	39.357	39.705	34.368	36.670
15	40.239	41.160	41.461	43.478	44.234
20	44.311	47.309	47.616	49.529	49.315
25	55.381	59.362	59.966	57.960	58.865
30	63.600	67.680	67.988	64.845	66.560
60	72.894	76.964	77.277	71.268	72.452
90	88.455	91.407	91.725	84.075	85.903
120	92.906	94.293	94.317	90.246	92.234

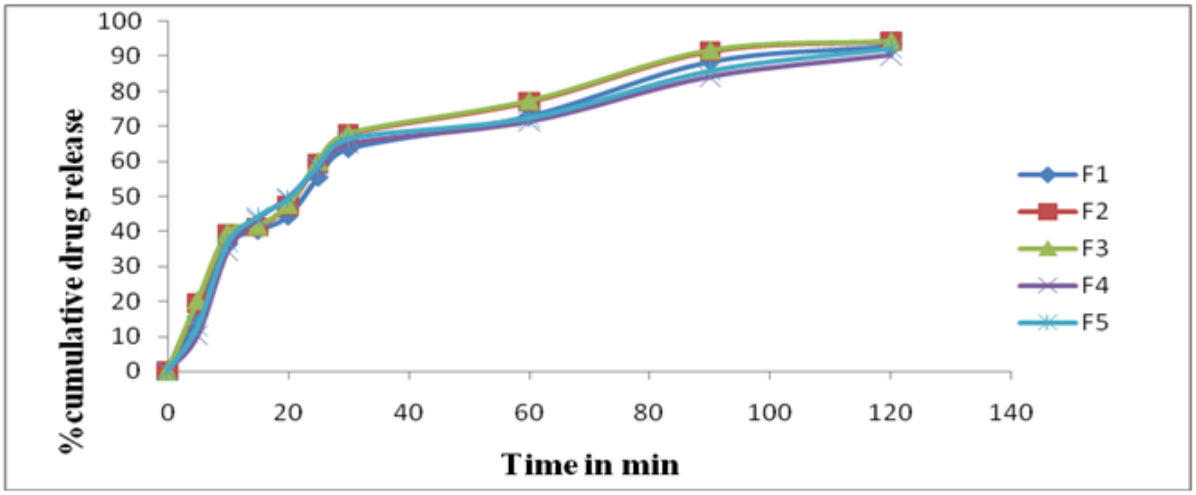

Fig no 5. Cumulative % drug release in 0.1N HCl capsule Batch F1 to F5

Table no 5. *In vitro* drug release in Ph 6.8 phosphate buffer

Time in min	F1	F2	F3	F4	F5
0	0.000	0.000	0.000	0.000	0.000
30	5.675	5.971	4.760	4.894	5..018
60	6.780	6.860	6.098	7.563	7.077
90	15.356	16.400	13.567	14.670	12.097
120	20.244	21.203	20.546	21.673	24.719
150	25.708	29.723	25.987	26.096	38.745
180	40.820	42.820	43.342	44.450	46.377
210	49.786	51.087	50.651	51.045	51.586
240	53.90	54.884	53.078	54.562	55.654
270	60..546	62.752	61.503	61.906	60.580
300	67.342	68.245	65.823	66.291	64.988
330	72.998	74.381	70.056	71.899	69.824
360	78.935	79.450	76.234	77.340	75.119
390	86.231	87.571	81.672	82.650	83.920
420	92.454	93.159	87.074	87.890	90.749
450	96.230	98.669	93.340	94.346	92.571

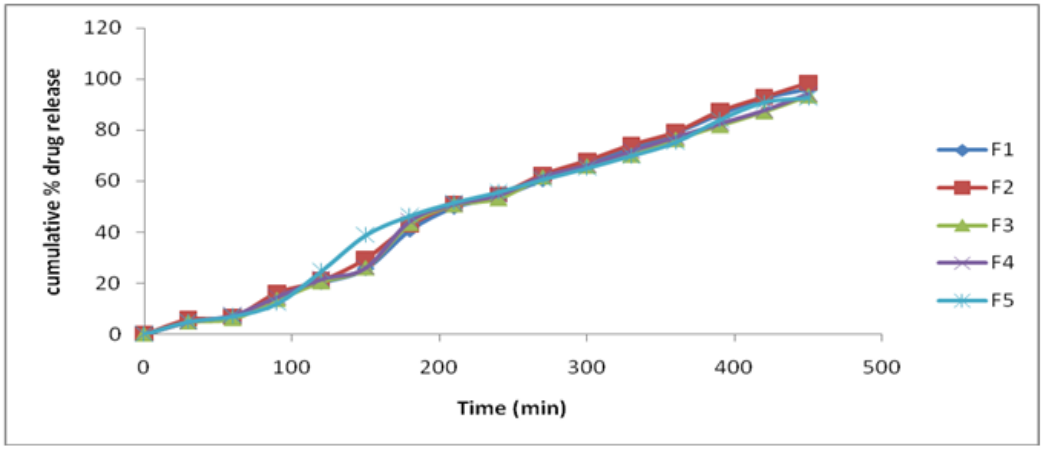

Fig no 6. Cumulative % drug release in ph 6.8 phosphate buffer capsule Batch F1 to F5

***In-Vitro* Release Kinetic studies:-**

To know the release mechanism and kinetics of formulations were attempted to fit into mathematical models and n, R^2 values for zero order, first order, matrix Korsmeyer- Peppas and Hixson Crowell models were represented in Table No 6.

Table no 6. *In-vitro* Drug Release Kinetics of drug Release in 0.1N Hcl

Models	R^2 value	K value
Zero order	0.4681	1.0308
First order	0.9618	- 0.0239
Matrix	0.9565	9.7537
Korsmeyer- Peppas	0.9577	11.924
Hixson Crowell	0.8796	-0.0057

Observation of all the R^2 values indicated that the highest R^2(0.9618) and n(0.4581) values were found for First order release which are shown in Table No.6 and Hence best fit model was found to be First order.

Table no 7. *In-vitro* Drug Release Kinetics of drug Release in ph 6.8 phosphate buffer

Models	R^2 value	K value
Zero order	0.9956	0.0002
First order	0.9957	0.0000
Matrix	0.9133	0.0038
Korsmeyer- Peppas	0.9869	0.0001
Hixson Crowell	0.9956	0.0000

Observation of all the R^2 values indicated that the highest R^2(0.9869) and n(1.1498) values were found for Korsmeyer- Peppas release which are shown in Table No.7 and Hence best fit model was found to be Korsmeyer- Peppas.

Drug-excipient compatibility studies:-

FTIR Spectroscopy:-

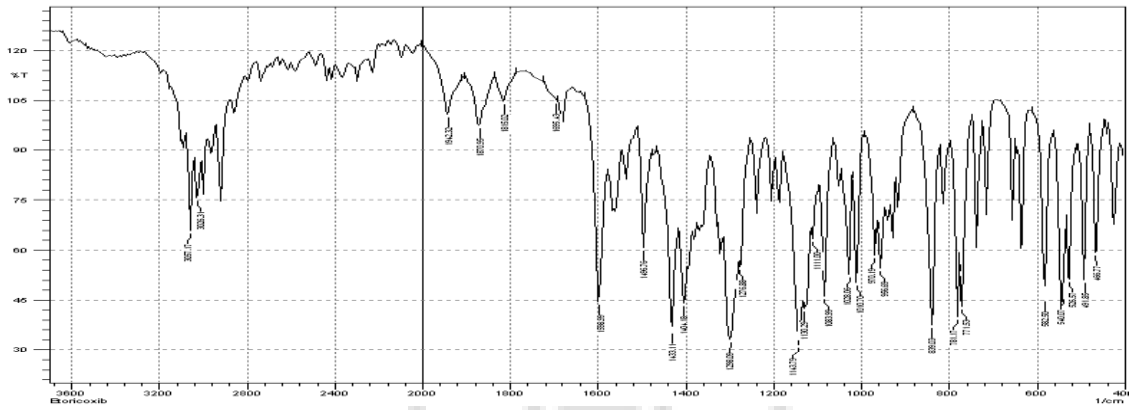

Fig no 7. FTIR spectrum of pure Etoricoxib

Table no 8. Interpretation of FTIR spectrum of Etoricoxib

Sr. No.	Wavenumber (cm^{-1})	Functional Group
1	**9992**592.9**962.66**	C=N stretching
2	1430.0	S=O stretching
3	1299.4,	S=O stretching
4	1136.8, a	S=O stretching
5	1089.6	S=O stretching
6	834.0	C–Cl stretching

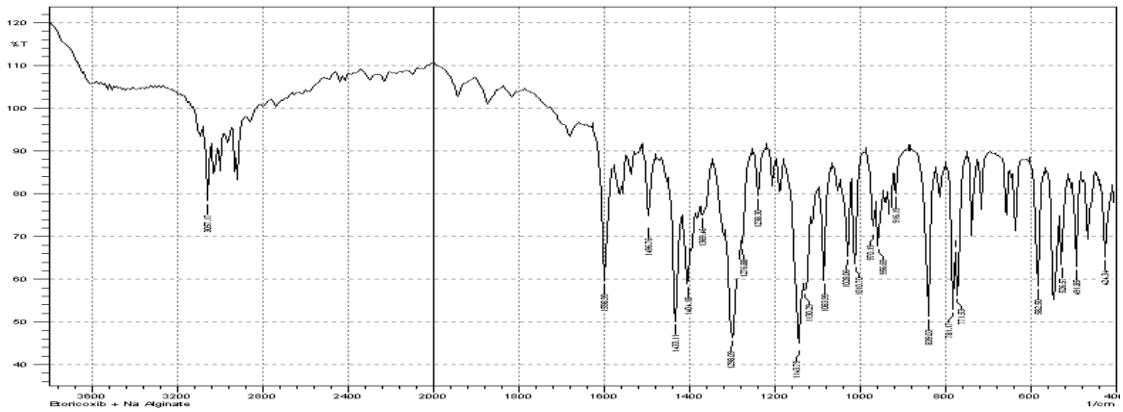

Fig no 8. FTIR spectrum of Etoricoxib+Sodium alginate

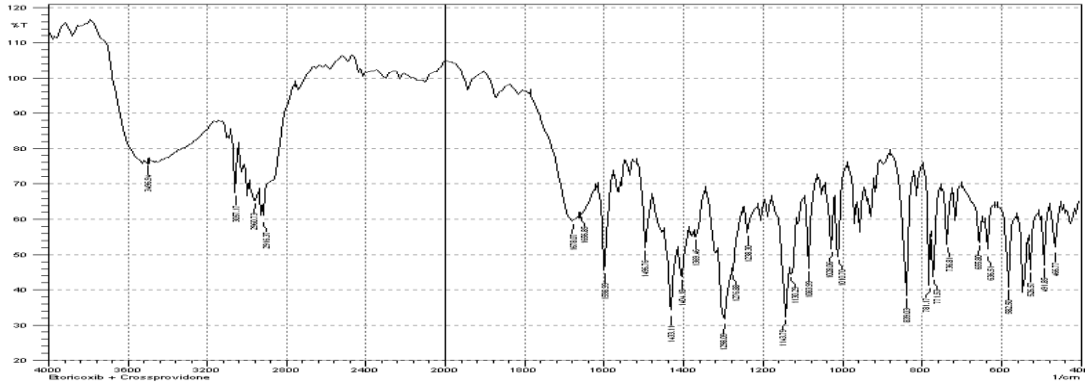

Fig no 9. FTIR spectrum of Etoricoxib+Crosspovidone

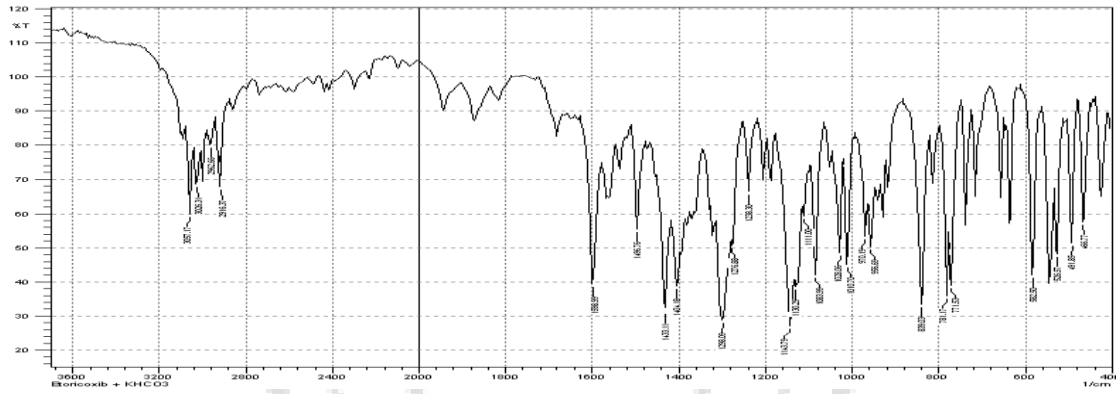

Fig no 10. FTIR spectrum of Etoricoxib+KHCO3

Stability studies:-

The results of accelerated stability studies reveal that the optimized capsule-in-a-capsule formulation did not show any change in appearance, drug content and *in vitro* release characteristics during stability study.

Table No.9:- Stability study

Parameter	**Before Stability study**	**After Stability study**
Appearance	Normal	No signs of leakage but capsules became little softer
% Drug content of liquid-filled-capsules (LFC-3)	98.15%	96.37%
% Drug content of beads-filled-capsules (BFC-2)	98.87%	96.45%
% Drug release at the end of 30min and 12h	98.50% and 98.78%	94.31% and 98.66%

CONCLUSION

Study concluded that Capsule in capsule delivery system was ideally suited for combination or dual release products. A novel biphasic drug delivery system was successfully developed by filling smaller beads- filled capsule into a bigger liquid dispersion-filled-capsule body. The best fast releasing liquid dispersion Formulation-3 and slow releasing beads Formulation- 2 of Etoricoxib were selected through *in vitro* dissolution studies. The capsule-in-capsule formulation showed 94.31% immediate release of drug at the end of 30 min and 98.66% sustained release of drug at the end of 12hr. From stability studies, it was concluded that formulation was stable at 40°C/75% RH for a period of 3 months as per ICH guidelines.

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REFERENCES

1. Haung J, Kao H,. The pH-dependent biphasic release of azitromydine from a layered composition of PVP disks and spheres. Toronto, Ontario, Canada, journal of Controlled Release. 2000, 67(1): 45-54.
2.Khan A.W, Ahmed M .G ,Formulation and Evaluation of Sustained release Capsules of Terbutaline Sulphate .Int.Res,J Pharm 2011;2(1) 249-55.3.
3.www.wikipedia.com
4..A.Srinivasa Rao et al., Int J Pharm Biomed Res 2013, 4(3), 170-176 .
5.Hariprasanna, R.C., Qamar Jamal Ahmad, Upendra kulkarni, *Asian J Biochem Pharm Res* 2011, *2*, 552-561
6.Varahala Setti, M.L., Vijaya Ratna, J., *Asian J Pharm* 2009, *3*, 252-256.
7.Brittain HG. Analytical profiles of drug substances and excipients, Vol.25. Academic Press, UK; 1998:39-84.