



Formulation and Evaluation of Gastroretentive Floating Drug Delivery System of Ketoprofen

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Abstract

Ketoprofen is an anionic non-steroidal anti-inflammatory drug (NSAID), was selected as a model drug. Different tablets formulations were prepared by wet granulation method. Required quantity of drug, and low-density polymer (HPMC K4M, HPMC K100M and Ethyl cellulose), alkalizing agent (sodium bicarbonate), and acidifying agent (citric acid) were passed through 60 mesh sieve and mixed thoroughly. Then, granulating agent (PVP) was added slowly with uniform mixing the get a wet mass. The wet mass was passed through sieve no 16 to obtain wet granules. The granules were dried at 50 ° C for 5 to 6 hrs in tray dryer. The dried granules were passed through sieve.no.22, after blending with lubricants (talc) was compressed using tablet compression machine (11mm diameter punches). Each tablet contained 200mg of Ketoprofen and other pharmaceutical ingredients. All the ten formulations were evaluated for various tests like thickness, hardness, friability, weight variation, tablet density, swelling index, drug content, dissolution, micromeritic properties and other kinetic parameters etc. Drug excipient interactions were studied with IR technique which found that there was no interaction between them. Total floating time and Buoyancy lag time were found to be satisfactory for 10th formulation.

Keywords: Ketoprofen, HPMC, Ethyl cellulose, Buoyancy, sodium bicarbonate, swelling index.

INTRODUCTION

Floating dosage forms are emerging as a promising novel dosage forms. Floating dosage forms can be prepared as tablets, capsules by incorporating suitable excipients as well by adding certain

gas-generating agents, which in turn give the buoyancy to the dosage form in gastrointestinal fluids.

Drug delivery systems are used for maximizing therapeutic index of the drug and reduction in side effects due to site-specific drug delivery. With the recent developments and advances in pharmaceuticals, frequently taken medicaments are incorporated in a single unit dosage form. This reduces the frequency of administration of medicament to the patient. The real challenge in the development of a controlled drug delivery system is not just to sustain the drug release but also to prolong the presence of the dosage form in the stomach or the upper small intestine until all the drug is completely released in the desired period of time.^{1,2}

The residence of a drug delivery system in the upper part of the gastrointestinal tract (GIT) can be accomplished by several drug delivery systems, such as intragastric floating systems,³ swelling and expandable systems,⁴ bioadhesive systems,⁵ modified shape systems,⁶ high-density systems,⁷ delayed gastric-emptying systems⁸ and low-density super porous systems.⁹ This review deals with floating dosage forms, an oral novel drug delivery system. In general, the drug release is governed by various polymers, which are used in the formulation. These polymers entrap the drug material in the matrix form or form a membranous sheath around the drug. The polymer in either case controls the release rate of drug by diffusion or by erosion method. Such drug delivery systems are termed as controlled drug delivery systems, which release the drug(s) with a predictable kinetics. Other approaches and materials that have been reported are highly swellable hydrocolloids and light mineral oils, a mixture of sodium alginate and sodium bicarbonate, multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinyl pyrrolidone coated with hydroxypropyl methylcellulose (HPMC) and floating systems based on ion-exchange resin technology.¹⁰

Excipients used most commonly in these systems include HPMC, polyacrylate polymers, polyvinyl acetate, polyethylene glycol (PEG)-6000, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. Drugs used in the formulation of floating dosage forms and some of the marketed preparations are given in table 1 and table 2.

Table 1: Drugs used in the formulation of floating dosage forms

Dosage forms	Drug
Floating microspheres	Aspirin, Griseofulvin, P- Nitroaniline, Ibuprofen, Terfenadine and Tranilast
Floating granules	Diclofenac sodium, Indomethacin and Prednisolone
Films	Cinnarizine
Floating capsules	Chlordiazepoxide hydrogen chloride, Diazepam, Furosemide, Misoprostol, L- DOPA, Benserazide, Ursodeoxycholic acid and pepstatin.
Floating tablets and pills	Acetaminophen, Acetylsalicylic acid, Ampicillin, Amoxicillin trihydrate, Atenolol, Diltiazem, Fluorouracil, Isosorbide Mononitrate, P- aminobenzoic acid, Piretanide, Theophylline, and Verapamil hydrochloride.

Table: 2 some of the marketed preparations

Drug	Brand name
Diazepam floating capsules	Valrelease
Benserazide and L-DOPA	Madopar
Aluminium – Magnesium antacid	Topalkan

Taking these factors into consideration, investigators formulated a novel drug delivery system for controlled drug delivery at the stomach level, termed as floating tablets or Hydrodynamically Balanced Systems (HBS) or gastroretentive drug delivery systems to prolong the residence of the dosage forms in the stomach or somewhere in the upper small intestine until all the drug is released for the desired period. Gastroretentive systems can remain in the gastric region for several hours, and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Gastroretention helps provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

MATERIALS AND METHODS

Ketoprofen was obtained as gift sample from Biological Pvt. Ltd. Hyderabad India. Hydroxypropylmethylcellulose K4M (HPMC K4M), HPMC K100M and ethyl cellulose were purchased from Colorcon Asia Pvt. Ltd., Goa. Sodium bicarbonate, Citric acid, polyvinyl pyrrolidone were obtained commercially from S. D. Fine Chemicals, (Mumbai, India).

Preparation of gastro retentive floating tablets of Ketoprofen:

Floating tablets containing Ketoprofen were prepared by wet granulation technique using variable concentrations of HPMC K4M, HPMCK100M, and Ethyl cellulose with sodium bicarbonate. Different tablets formulations were prepared by wet granulation method. Required quantity of drug, and low-density polymers (HPMC K4M, HPMC K100M and Ethyl cellulose), alkalizing agent (sodium bicarbonate), and acidifying agent (citric acid) were passed through 60 mesh sieve and mixed thoroughly. Then, granulating agent (PVP) was added slowly with uniform mixing to get a wet mass. The wet mass was passed through sieve no 16 to obtain wet granules. The granules were dried at 50 ° C for 5 to 6 hrs in tray dryer. The dried granules were passed through sieve.no.22, after blending with lubricants (talc) and were compressed using tablet compression machine (11mm diameter punches). Each tablet contained 200mg of Ketoprofen and other pharmaceutical ingredients. The formulae of 10 formulations are mentioned in table 3.

Physical characterization:

The fabricated tablets were characterized for weight variation (n=20), hardness (n=6, Monsanto hardness tester), thickness using a screw-gauge micrometer (Campbell Electronics, Mumbai, India) and % friability (n=20, Roche friabilator, Electrolab, Mumbai, India), and tablet density.

Assay of tablets:

Twenty tablets from each batch were weighed and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, A portion of the sample was filtered through 0.45 m membrane filter and analyzed by Shimadzu UV-1700 UV/Vis double-beam spectrophotometer (Kyoto, Japan) at 260 nm.

Table: 3 Composition of Ketoprofen Floating Tablets

INGREDIENTS	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9	FT10
Ketoprofen	200	200	200	200	200	200	200	200	200	200
HPMC K4M	200	-	-	100	100	-	100	50	50	100
HPMC K100M	-	200	-	100	-	100	50	100	50	75
Ethyl cellulose	-	-	200	-	100	100	50	50	100	25
Sodium bicarbonate	90	90	90	90	90	90	90	90	90	90
Citric acid (anhydrous)	15	15	15	15	15	15	15	15	15	15
PVP-K-30	22	22	22	22	22	22	22	22	22	22
Magnesium Stearate	6	6	6	6	6	6	6	6	6	6
Talc	7	7	7	7	7	7	7	7	7	7

All quantities were in milligrams.

All the batches contained 1% w/w talc and 0.5% w/w magnesium stearate

Floating capacity:

The *in vitro* buoyancy was determined by floating lag times as per the method described by Rosa *et al*¹¹. The tablets were placed in a 100 ml beaker containing 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The experiments were conducted in triplicate. Total floating times were measured during *in vitro* dissolution studies.

***In vitro* dissolution studies:**

All the ten formulations of floating tablets of ketoprofen were subjected to *in vitro* release studies these studies were carried out using USPXXIII tablet dissolution apparatus (Electrolab, TDT-06P, Mumbai, India), in 900 ml of both 0.1N HCL (PH 1.2) and Phosphate buffer Ph 6.8. at 37±0.5° and 50 rpm A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 24 h, and the samples were replaced with fresh dissolution medium. The samples were filtered through 0.45 m membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 260 nm using a Shimadzu UV-1700 UV/Vis double-beam spectrophotometer (Kyoto, Japan). Duration of time the tablet

constantly float on dissolution medium were noted as total floating time

Drug Release

Dissolution tests were conducted in triplicate for all formulations in a USPXXIII tablet dissolution apparatus (Electrolab, TDT-06P, Mumbai, India). The dissolution medium was 900 ml 0.1N HCl (pH 1.2) at $37 \pm 0.5^\circ$ at 50 rpm. At predetermined time intervals, 5 ml samples were withdrawn and sink conditions maintained. The samples were analyzed for drug release by measuring the absorbance at 260 nm using spectrophotometric method Shimadzu UV-1700 UV/Vis double-beam spectrophotometer (Kyoto, Japan). The drug release data was analyzed to study release kinetics using zero order, first order, Korsemeyer- Peppas and Higuchi equations.^{12,13}

Zero order equation

$$\% \text{ Drug released} = kt \dots\dots\dots(1)$$

Where, k = constant, t = time

First order equation

$$\log \% \text{ unrelease d} = \frac{kt}{2.303} \dots\dots\dots(2)$$

Korsemeyer- Peppas equation,

$$\text{Log drug released} = \log k + n \log t \dots\dots\dots(3)$$

Where, n = release exponent

Higuchi's equation

$$\% \text{ Drug released} = kt^{0.5} \dots\dots\dots(4)$$

Per cent dissolution efficiency and mean dissolution time were calculated for all formulations.^{14,15}

Determination of swelling index

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using The dissolution medium was 900 ml 0.1N HCl (pH 1.2) at $37 \pm 0.5^\circ$ at 50 rpm , After 0.5, one, two, three, four, and five, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, AX 120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.¹⁶

$$\text{Swelling index} = \frac{\text{(Wet weight of tablet - Dry weight of tablet)}}{\text{Dry weight of tablet}} \dots\dots\dots(5)$$

***In vitro* buoyancy studies:**

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al*¹¹. The tablets were placed in a 100 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time.

Drug polymer interaction:

Drug-polymers interaction was studied by using FTIR (Shimadzu, Japan.Model-8400S).

RESULTS AND DISCUSSION

When the floating matrix tablets containing gas-generating agents were exposed to 0.1N HCl, hydrochloric acid reacted with sodium bicarbonate in the floating tablet inducing CO₂ formation. The generated gas was entrapped into the matrix of swollen polymer matrix and well protected by gel formed by hydration of polymers, which led to floating of the dosage forms.¹⁷

Table: 4 Evaluation of Physical Parameters of Floating Tablets

Tablets Batch	Weight variation test (%)	Friability (%)	Hardness (kg/cm ²)	Thickness (mm)	Drug Content (%)
FT1	± 1.75	0.92	5.6 ±0.47	4.08 ± 0.2	98.02
FT2	±3.52	0.72	4.5 ±0.63	4.16 ±0.010	97.01
FT3	±2.15	0.91	6.4 ±1.27	4.14 ±0.012	99.53
FT4	±1.56	0.86	5.1 ±0.03	4.12 ±0.06	98.01
FT5	±3.54	0.79	4.3 ±0.83	4.16 ±0.011	97.04
FT6	±1.42	0.86	5.1±0.03	4.18 ±0.012	98.40
FT7	±2.11.	0.78	4.3 ±0.83	4.15 ±0.010	97.11
FT8	±1.89	0.81	6.4 ±1.27	4.10 ±0.012	99.55
FT9	±2. 56	0.96	5.1 ±0.03	4.11 ±0.06	99.01
FT10	±2.04	0.75	4.3 ±0.83	4.20±0.011	99.69

Table: 5 Micrometric properties of powder blend

Powder blend	Angle of Repose ($^{\circ}$)	Loose Bulk Density (g/ml)	Tapped Bulk Density (g/ml)	Compressibility Index (%)	Total Porosity (%)
FT1	24°.30'	0.130	0.155	16.13	15.78
FT2	26°.77'	0.110	0.130	15.67	20.00
FT3	25°.28'	0.090	0.102	14.48	37.50
FT4	28°.56'	0.105	0.126	16.30	26.31
FT5	29°.88'	0.129	0.146	15.41	27.77
FT6	25°.30'	0.114	0.135	14.30	12.50
FT7	26°.47'	0.132	0.148	12.76	35.00
FT8	24°.28'	0.135	0.154	13.47	13.04
FT9	26°.56'	0.144	0.162	12.34	20.83
FT10	28°.88'	0.106	0.120	15.91	10.00

Table: 6 Swelling Index of Tablets of Batch FT1 to FT10

Time	Swelling Index of Tablets of Batch FT1 to FT10									
	FT1	FT2	FT3	FT4	FT5	FT6	FT7	FT8	FT9	FT10
1 hr	32	33	31	40	35	29	36	48	30	42
2 hrs	39	38	38	51	42	36	46	59	41	51
3 hrs	41	43	44	62	49	48	56	65	46	67
4 hrs	49	49	52	73	57	59	64	78	54	76
5 hrs	56	65	68	90	68	62	77	82	60	91

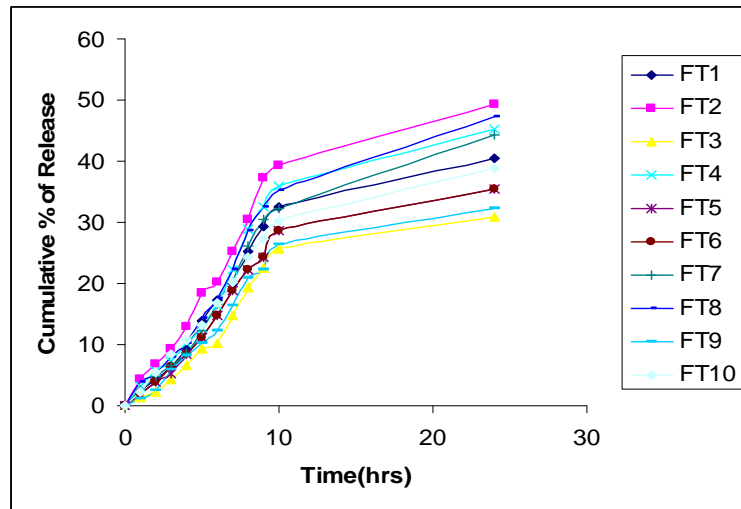


Fig no 1 : In vitro dissolution profile for tablets of batches ft1 to ft10 (using 0.1 N Hcl as dissolution medium)

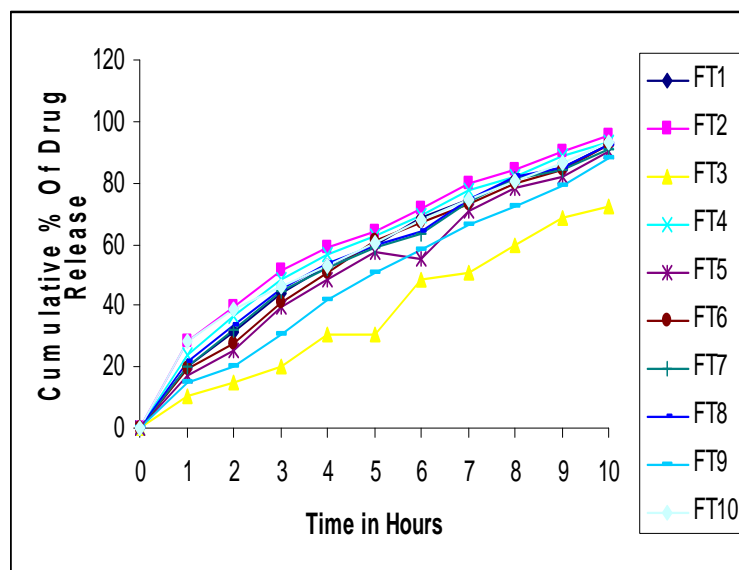


Fig no 2: In vitro dissolution profile for tablets of batches ft1 to ft10 (using phosphate buffer ph 6.8 as dissolution medium)

INVITRO BUOYANCY STUDY OF FORMULATION FT10



At initial time



After 25 Seconds



After 45 Seconds



After 10 Hours

Fig no: 3 Invitro buoyancy study of best formulation

Fig no: 4. I.R Spectrum of Ketoprofen

SHIMADZU

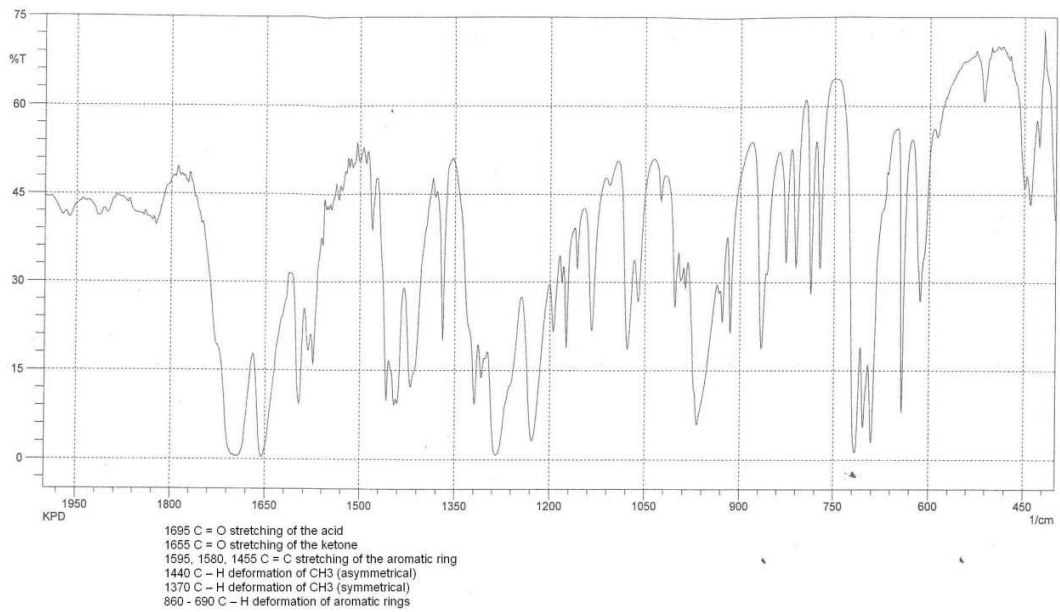


Fig no: 5. I.R Spectrum of Ketoprofen and HPMC K4M

SHIMADZU

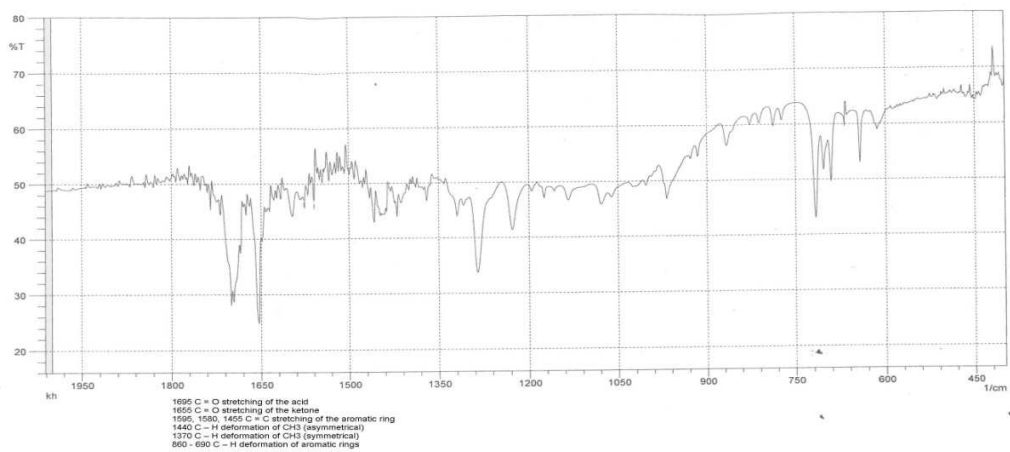


Fig no: 6. I.R Spectrum of Ketoprofen and HPMC K100M

SHIMADZU

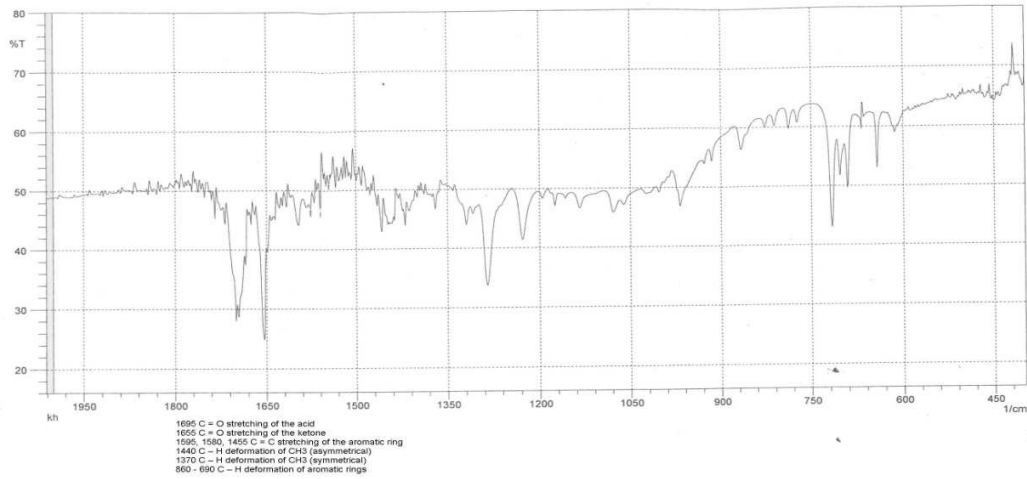
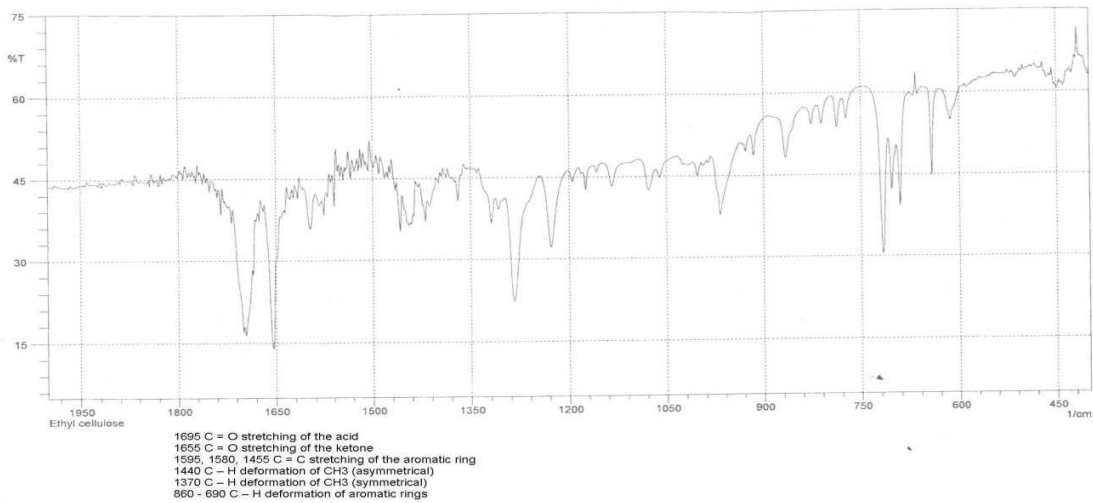


Fig no: 7. IR Spectrum of Ketoprofen and Ethyl Cellulose.

SHIMADZU



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