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Research Article

Formulation And Evaluation Of Fast Dissolving Tablets By Addition Of Different Concentrations Of Superdisintegrant And By Effervescent Technology.

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Abstract

Ketoprofen is NSAID drug used for osteoarthritis and rheumatoid arthritis. The major problem with this drug is very low solubility in biological fluids. Therefore solid dispersion of Ketoprofen with PVP K30 in different weight ratios were prepared to increase its water solubility. The solid dispersions were evaluated by solubility study, drug content, in-vitro drug release, dissolution efficiency and characterized by FT-IR. The Ketoprofen SD with PVP K30 (1:4) ratio showed maximum amount of drug release it was selected for Fast Dissolving Tablet formulation. The Tablets were prepared by by addition of different concentrations of superdisintigrant and By Effervescence Technology, The tablets were evaluated for Pre-Compression and Post-Compression Studies, among all the formulations F5 showed least disintegration time and 99.60% of drug release in 20 minutes. Stability study of F5 was carried out at 40^0c and 75% RH for three months. it confirms there is no significant change in the formulation.

Keywords: Ketoprofen, Solid dispersion, Fast dissolving Tablets, Superdisintigrant, Effervescence Technology.

Introduction

Fast dissolving tablets disintegrate or dissolve quickly in the oral cavity, or swallowed without the need for the administration of water. leading to an increase in bioavailability by avoiding first pass liver metabolism. Fast disintegrating tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.These tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, rapimelts, porous tablets, quick dissolving etc. Recent developments in fast-dissolving tablets provide a convenient solution for patients who have difficulties in swallowing conventional tablets. These FDT turn into a soft paste or liquid form for easy swallowing and thus it is free of suffocation risk[1,2]. The primary beneficiaries for FDTs are pediatric and geriatric patients, bedridden or developmentally disabled patients. The key properties of FDTs are fast absorption of water in to the core of the tablets and disintegration of associated particles into individual components for fast dissolution[3,4]. Ketoprofen [5-10] Thus, its availability seems to be dissolution rate limited. Ketoprofen is practically insoluble in water, The rate of dissolution can be increased by increasing the surface area of available drug by various methods like Micronization, Complexation and Solid dispersion [11] (SD). hence present study was carried out to enhance solubility and dissolution properties of Ketoprofen through the preparation of Solid Dispersions (SD) using PVP[12] as carriers at various proportions (1:1,1:2,&1:4) by using Solvent evaporation technique and the addition of different concentration of superdisintegrant such as crospovidone[13] and Effervascent agents like Citric acid and Sodium bicarbonate in combination in (2:3 ratio) were studied. U.V. Spectrophotometer method was selected for assay as well as in-vitro dissolution studies. The FTIR was used to characterize the solid state of

solid dispersions. A marked increase in dissolution rate was observed with all solid dispersions among them the optimized solid dispersion was selected for tablet formulation. The tablets prepared by direct compression technique on 8 station tablet machine (Rimek Mini press-II,Karnavati Engineering Ltd,Ahmedabad).The tablets were evaluated for pre-compression and post-compression parameters. Among all tablet formulations, F5 which containing solid dispersion of Ketoprofen and Crospovidone as a superdisintegrant showed least disintegration time and faster dissolution.

MATERIALS AND METHODS:

Ketoprofen was procured from Concept Pharmaceuticals, Aurangabad. Polyvinylpyrollidone K-30 , Crospovidone, Avicel PH 102. Lactose, Dextrose M/s Healer's Labs Pvt. Ltd., Baddi, Methanol LR, Acetone LR, Sodium Bicarbonate, Citric Acid, S.D.Fine Chemicals Pvt. Ltd., Mumbai,And all other materials used were of pharmaceutical grade.

PREPARATION OF SOLID DISPERSIONS OF KETOPROFEN:

Ketoprofen solid dispersions were prepared by solvent evaporation method using carriers (i.e. PVP K-30) in proportions, viz. 1:1, 1:2, 1:4 (Drug: Carrier). Methanol is selected as common solvent for solid dispersion. The respective amount of carrier was dissolved in methanol 20 ml and ketoprofen was added in parts with continuous stirring. The solvent was then removed by evaporation. The prepared solid dispersion were pulverized and shifted through sieve no. 100 and stored over a fused calcium chloride in a desiccator for further use.

EVALUATION OF SOLID DISPERSIONS:

The prepared solid dispersions were evaluated for solubility studies, percent drug content, dissolution efficiency, *in-vitro* drug release and Fourier transform infrared (FTIR).

Determination of solubility of solid dispersions:

Ketoprofen, solid dispersions equivalent to 10 mg of Ketoprofen were added to 10 ml of Sorenson's buffer pH 6.8 in a 10 ml volumetric flask. The volumetric flasks were capped properly and shaken at 25^0 and 37^0 C in a temperature controlled water bath (Shaking water bath) for 48 h. Resultant samples containing undissolved solid dispersions suspended in the volumetric flask were filtered through 0.45µm filters, suitably diluted with Sorenson's buffer pH 6.8 and analyzed by UV spectrophotometer at 260 nm.

Determination of drug content:

Drug content was calculated by dissolving solid dispersions equivalent to 100 mg Ketoprofen in 10 ml of methanol, filtered using 0.45µm Whatman filter paper, suitably diluted with Sorenson's buffer (pH 6.8) and analyzed by using UV spectrophotometer against Sorenson's buffer as blank.

In-vitro drug release:

Accurately weighed preparations equivalent to 100 mg of Ketoprofen were added to 900 ml of dissolution medium in USP II Paddle type apparatus and stirred at speed of 50 rpm at 37 ± 0.5^0 C. 5 ml aliquots were withdrawn at 5, 10, 15, 30, 45, 60 minutes and replaced by 5 ml of fresh dissolution media. The collected samples were analyzed after filtration and dilution at 260 nm using UV-visible spectrophotometer against the blank. Drug release studies were carried out in triplicate. The dissolution of pure Ketoprofen was done similarly. The release profile data was analyzed for cumulative percent dissolved at different time intervals and for dissolution efficiency at 15 and 30 minutes.

Fourier transform infrared spectroscopy:

Fourier Transform Infrared spectra were recorded on samples prepared in potassium bromide (KBr) disks. Samples were prepared in KBr disks by means of a hydrostatic press. The scanning range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

FORMULATION OF FAST DISSOLVING TABLETS:

Fast dissolving tablets containing selected solid dispersion (KPVP-4) were prepared by direct compression method using single punch tablet machine to produce convex faced tablets weighing 500 mg each with a diameter of 11 mm. The formulations were developed by using different techniques. By Addition of the superdisintegrant Crospovidone and Citric acid and Sodium bicarbonate in combination in (2:3 ratio) in varying concentration (1-5%) were used to prepare the tablets. All the ingredients were passed through sieve no. 60 and were co- grounded in a glass pestle motor. The mixed blend of excipients was

compressed by direct compression technique on 8 station tablet machine (Rimek Mini press-II,Karnavati Engineering Ltd,Ahmedabad) to produce convex faced tablets weighing 500 mg each with a diameter of 11 mm.

Table-1: Formulation of Fast Dissolving Tablet Using Crospovidone.

INGRADIENTS IN (mg)	F1	F2	F3	F4	F5
KPVP4	200	200	200	200	200
Crospovidone	5	10	15	20	25
Lactose	70	70	70	70	70
Dextrose	70	70	70	70	70
Avicel PH 102	135	130	125	120	115
Talc	10	10	10	10	10
Mg. Stearate	10	10	10	10	10
Cardamom flavor	QS	QS	QS	QS	QS

Table-2: Formulation of Fast Dissolving Tablet Using Effervescent Agents

INGRADIENTS IN (mg)	F6	F7	F8	F9	F10
KPVP4	200	200	200	200	200
Citric acid	2	4	6	8	10
Sodium bicarbonate	3	6	9	12	15
Lactose	70	70	70	70	70
Dextrose	70	70	70	70	70
Avicel PH 102	135	130	125	120	115
Talc	10	10	10	10	10
Mg. Stearate	10	10	10	10	10
Cardamom flavor	QS	QS	QS	QS	QS

Table-3: Dissolution Efficiency of Ketoprofen-PVP K30 Solid Dispersions.

FORMULATION	Dissolution Efficiency (%)	
	DE 15	DE 30
Pure drug	2.92	6.46
KPVP1 (1:1)	12.91	25.83
KPVP2 (1:2)	30	47.92
KPVP4 (1:4)	44.16	63.33

Table-4: Percent Drug Content of Ketoprofen-PVP K-30 Solid Dispersions

SR.NO.	Formulation Number	%Drug Content
1	KPVP1(1:1)	99.36±0.50
2	KPVP2(1:2)	98.61±0.58
3	KPVP4(1:4)	98.51±0.57

Data are expressed as mean ± S.D. (n = 3)

Table-5: Characterization of Fast Dissolving Tablets.

Formulation	Thickness(mm)	Weight(mg)	Friability (%)	Hardness(Kg/cm²)
F1	6.34±0.01	499.33±3.21	0.51±0.000208	3.43±0.11
F2	6.37±0.03	498.66±0.57	0.71±0.000994	3.13±0.15
F3	6.34±0.03	501.66±2.08	0.76±0.000466	3.16±0.15
F4	6.33±0.03	499.33±1.52	0.51±0.002573	3.06±0.20
F5	6.34±0.03	501.33±1.52	0.47±0.000396	3.3±0.22
F6	6.34±0.03	498.66±0.57	0.76±0.000978	2.66±0.15
F7	6.36±0.03	498.66±1.52	0.67±0.000415	2.8±0.17
F8	6.34±0.01	499.33±2.08	0.84±0.000514	2.56±0.20
F9	6.36±0.04	498.66±3.05	0.91±0.000212	2.5±0.17
F10	6.32±0.33	500.66±1.52	0.95±0.000383	2.7±0.26

Data are expressed as mean ± S.D. (n = 3)

Table-6: Characterization of Fast Dissolving Tablets.

Formulation	Disintegration time (Seconds)	Wetting time (Seconds)	Dispersion time (Seconds)
F1	47.48±1.87	60.04±3.82	67.46±2.54
F2	36.01±1.65	42.94±3.04	54.35±2.62
F3	29.02±1.70	31.83±2.84	42.83±1.18
F4	27.71±1.14	29.67±1.47	33.69±2.08
F5	25.68±1.41	27.44±1.40	30.91±1.68
F6	68.31±2.26	59.38±1.80	69.56±1.91
F7	51.65±2.11	49.47±2.94	56.48±3.13
F8	39.41±2.20	43.66±2.03	49.44±3.78
F9	31.52±3.02	36.40±1.42	42.74±2.55
F10	29.16±1.74	31.11±2.14	34.19±1.93

Data are expressed as mean ± S.D. (n = 3)

Table-7: Drug content in the Fast Dissolving Tablets of Ketoprofen

Formulation	Drug content (mg per tablets)	Drug content(%)
F1	49.24±0.37	98.48±0.75
F2	49.42±0.38	98.85±0.77
F3	49.19±0.35	98.38±0.71
F4	49.71±0.17	99.43±0.35
F5	50.36±0.02	100.73±0.05
F6	48.99±0.18	97.98±0.37
F7	49.15±0.41	98.3±0.83
F8	49.90±0.23	99.81±0.23
F9	49.02±0.23	98.05±0.47
F10	49.06±0.30	98.13±0.60

Data are expressed as mean ± S.D. (n = 3)

Table-8: Fit of various kinetics Models for fast dissolving Tablets of Ketoprofen

Formulation Code	Zero order				First order				
	Intercept	R2	Slope	K (mg/min)	Intercept	R2	Slope	K (min^{-1})	t1/2
F1	18.78	0.81	3.45	7.94	1.91	0.94	0.03	0.06	10.03
F2	20.05	0.82	3.76	8.65	1.93	0.97	0.03	0.08	7.71
F3	22.67	0.8	3.96	9.12	1.93	0.97	0.04	0.11	6.26
F4	25.69	0.76	3.99	9.20	1.92	0.97	0.05	0.12	5.47
F5	29.06	0.76	4.29	9.88	1.99	0.97	0.09	0.20	3.30
F6	8.74	0.92	3.33	7.67	1.97	0.97	0.02	0.05	12.53
F7	19.4	0.77	3.15	7.25	1.90	0.90	0.02	0.05	12.03
F8	21.73	0.77	3.58	8.26	1.9	0.93	0.03	0.08	8.59
F9	25.26	0.75	3.86	8.89	1.89	0.96	0.04	0.10	6.54
F10	29.32	0.70	3.99	9.20	1.87	0.96	0.05	0.13	5.10

DETERMINATION OF *IN-VITRO* DRUG RELEASE:

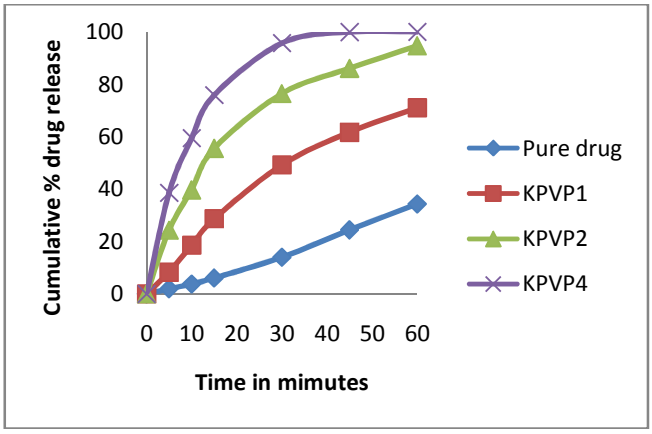

Figure1- Cumulative Percent Release of Ketoprofen from Solid Dispersions of Ketoprofen-PVP K-30 Systems.

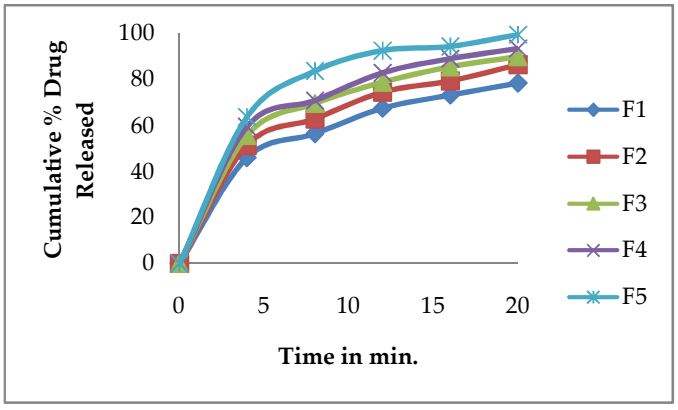

Figure-2: Zero Order Dissolution Release Profile of Ketoprofen from F1-F5.

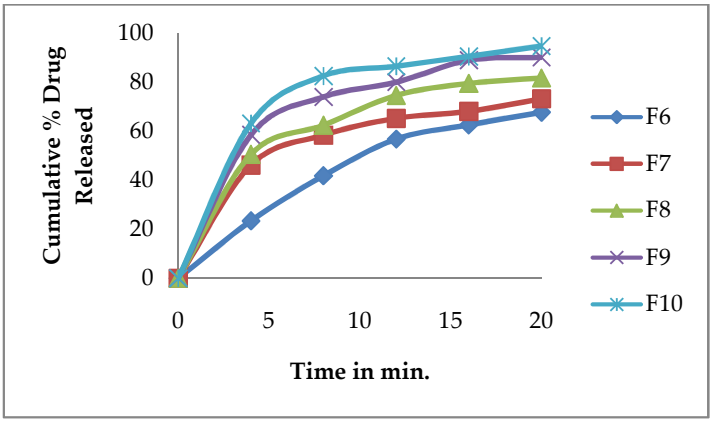

Figure-3: Zero Order Dissolution Release Profile of Ketoprofen from F6-F10.

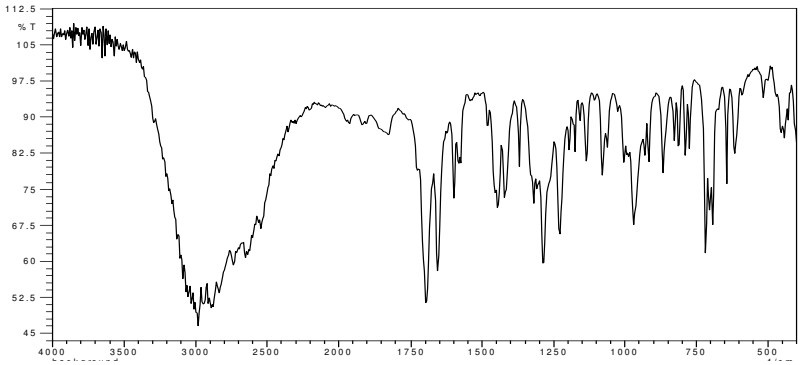

Figure-4: IR Spectra of Ketoprofen.

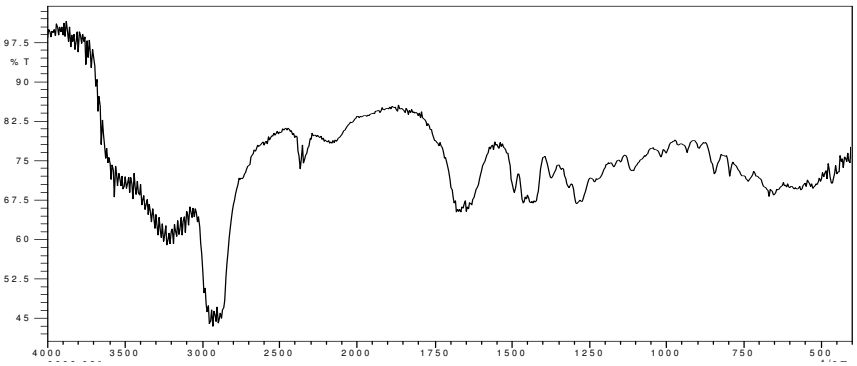

Figure-5: IR Spectra of Crospovidone.

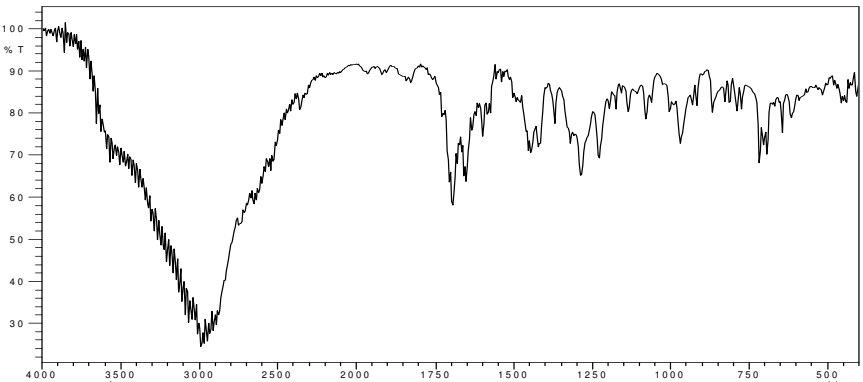

Figure-6: IR Spectra of Mixture of Drug and Crospovidone.

CHARACTERIZATION OF FAST DISSOLVING TABLETS:

After compression of powder, the tablets were evaluated for physical characteristics like thickness,weight,hardness, friability, disintegration time, wetting time, dispersion time and dissolution studies.

Uniformity of Weight:

As per IP, twenty tablets were taken and weighted individually and collectively using digital balance. The average weight of one tablet was calculated. The weight variation test would be satisfactory method of determining the drug content uniformity.

Hardnes:[14]

Hardness of the tablet of each formulation was determined using Pfizer hardness tester.

Friability:[15]

Friability of the tablets was determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inch in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (F %) is determined by the formula.

$$F\% = \left(1 - \frac{Wo}{W}\right) X100$$

Where, W_0 is initial weight of the tablets before the test and W is the weight of the tablets after test.

Disintegration Test:[16]

Disintegration of fast dissolving tablets is achieved by saliva in the mouth, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate *in vivo* conditions. A modified method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10-mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve. To determine disintegration time, 6 ml of Sorenson's buffer (pH 6.8), was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined.

Wetting Time:

The method was followed to measure tablet wetting time. A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish (ID = 65 cm) containing 6 ml of Sorenson's buffer (pH 6.8), A tablet was put on the paper, and the time for the complete wetting was measured. Three trials for each batch were performed and the standard deviation was also determined.

***In-vitro* Dispersion Time:**

In-vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of Sorenson's buffer (pH 6.8). Three tablets from each formulation were randomly selected and *in-vitro* dispersion time was performed.

***In-Vitro* Dissolution Studies:**[17-18]

In-vitro dissolution studies of formulation were carried out using USP paddle method at 50 rpm in 900 ml of Sorenson's buffer (pH 6.8) as dissolution media, maintained at 37±0.5^{0}C. 5 ml of aliquot was withdrawn at the specified time intervals, filtered through whatmann filter paper and analysed spectorphotometrically at 260 nm. An equal volume of fresh medium, which was prewarmed at same condition was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test.

Determination of drug content:

Drug content was calculated by dissolving solid dispersions equivalent to 100 mg Ketoprofen in 10 ml of methanol, filtered using 0.45µm Whatman filter paper, suitably diluted with Sorenson's buffer (pH 6.8) and analyzed by using UV spectrophotometer against Sorenson's buffer as blank.

Fourier transform infrared spectroscopy:

Fourier Transform Infrared spectra were recorded on samples prepared in potassium bromide (KBr) disks. Samples were prepared in KBr disks by means of a hydrostatic press. The scanning

range was 400 to 4000 cm^{-1} and the resolution was 4 cm^{-1}.

RESULT AND DISCUSSION:

In the present studies of FDTs of Ketoprofen were prepared and evaluated for achievement of fast action of active moiety. The tablets were prepared by direct compression method by using solid dispersion technology. Fast disintegration of tablets was achieved by using superdisintegrant and Citric acid and Sodium bicarbonate in combination (2:3 ratio) varying concentration (1-5%) were used to prepare the tablets. Ketoprofen is a water insoluble drug so this is necessary to increase the water solubility of the drug for that purpose firstly the solid dispersions of Ketoprofen were prepared with PVP K-30 (1:1,1:2 and 1:4) prepared and evaluated. The optimized solid dispersion was incorporated in FDTs. These prepared tablets were evaluated for their quality control parameter. Drug-polymer interaction study was carried out and evaluated for physical changes, change in absorption maxima and by FT-IR studies. So there was no significant shift in the peaks corresponding to the drug were observed. Both the drug and polymers were compatible with each other. Hence the drug and polymers can be successfully incorporated in the design of solid dispersion as well as fast dissolving tablet. The drug content of solid dispersions (KPVP1, KPVP2 and KPVP4) was found to be from 99.36±0.50 98.61±0.58 and 98.51±0.57 which shows the uniformity and reproducibility of the obtained method. It was observed that the saturation solubility of drug was increased by number of folds. By converting the drug into solid dispersion, due to the change in physical state of Ketoprofen from crystalline to amorphous, which was confirmed by the FT-IR studies. Dissolution efficiency of pure Ketoprofen and all the solid dispersion formulations at 15 minutes and 30 minutes were calculated. The dissolution efficiency increased in all the formulations. Among the formulations KPVP4 has shown maximum dissolution efficiencies of 44.12% and 63.30% at fifteen minutes (DE_{15}) and thirty minutes (DE_{30}) respectively. A disintegrant was incorporated in all the formulations to facilitate a breakup or disintegration of the tablet when it comes in contacts with water. Disintegrants drawing the water into the tablet causes swelling and the tablet bursts apart. In the formulation of fast dissolving tablet the superdisintegrant Crospovidone and Citric acid and Sodium bicarbonate in combination (2:3 ratio) varying concentration (1-5%) were used to prepare the tablets.The tablets with Crospovidone disintegrate faster than the tablets with the Citric acid and Sodium bicarbonate in combination. The disintegration time of all the formulations were found to be in between 25.68±1.41 sec to 68.31±2.26 Sec. The disintegration process of the tablet was fully dependable on nature and concentration of the used superdisintegrant and Effervascent agents.The *in-vitro* wetting time was also studied to know the time required for complete wetting of tablets when placed on tongue. The *in-vitro* wetting time of all the formulations were varied between 27.44±1.40 to 60.04±3.82 seconds. The swelling properties of the superdisintegrant was dependent upon their concentration and the results show that as the concentration of the superdisintegrant increased the time taken for swelling was reduced. The swelling time was rapid in Crospovidone. The tablets prepared with effervescent technology elaborates the carbon dioxide gas when the tablet comes in contact with little amount of saliva or water due to reaction between citric acid and sodium bicarbonate which results in breakup of tablets. The same sequence was observed in case of measurement of dispersion time of the tablet. All the Solid dispersions (SD_s) KPVP1, KPVP2 and KPVP4 prepared according to the formula shown in table: 1 and 2. Were found to be free flowing. Low values of C.V (<1.0%) in percent drug content indicated uniformity of drug content in each batch of solid dispersions. The dissolution profiles of various solid dispersions were shown in Fig:1. All the solid dispersions showed rapid dissolution of ketoprofen as compared to the pure drug. The dissolution rate of ketoprofen Increases with Increase in PVP-K30, up to 1:4 ratio of drug : carrier this increase in dissolution rate may be due to improved wettability of the carrier. In each case the dissolution was found to be obeying First order kinetics (R>0.9924). The dissolution rate constant (K_1) was calculated from the slope of the first order linear plots of the dissolution data. The dissolution efficiency (DE_{15}, DE_{30}) % value based on the dissolution data were calculated according to Khan [19]. The dissolution efficiency (DE_{15}, DE_{30}) % values of pure drug and SDs are shown in Table: 3.The ketoprofen: PVP-K30, 1:4 (KPVP-4) Solvent evaporation Method has shown maximum dissolution rate. The Percent Drug Content of (Ketoprofen-PVP K-30) Solid Dispersions were shown in Table: 4. Solid dispersions It was converted into Fast Dissolving

Formulations with the addition of different concentration of superdisintegrant crospovidone and Citric acid and Sodium bicarbonate in combination in (2:3 ratio) varying concentration (1-5%) were used to prepare the tablets. Among all tablet formulations, F5 which contains solid dispersion of ketoprofen and Crospovidone as a superdisintegrant showed faster dissolution rate than the tablets prepared shown in Fig: 2 and 3. The results of mean hardness, disintegration, The friability, Weight Variation of prepared tablets are shown in Table:5,6 and 7.The Best Fit of various kinetics Models for fast dissolving Tablets of Ketoprofen is shown in Table:8. The FT-IR of various Solid dispersions revel all the peaks of the drug. As it can be seen, a strong absorption peaks at 1696 and 1655 cm^{-1} occurs in the IR spectrum of Ketoprofen. So there is no significant shift in the peak corresponding to the drug or the polymer was observed in the solid dispersions. The results clears that there is no chemical interaction in with the chemical entity of Ketoprofen, this is shown in Fig: 4, 5 and 6. In order to determine the change in the *in-vitro* release profile on storage stability study of F5 was carried out at 40^0c and 75% RH for three months, no visible physical changes were observed in the formulation withdrawn from the humidity chamber.

CONCLUSION:

From the above observations it is concluded that the solid dispersion technique could be successfully used to improve the water solubility and Dissolution rate of ketoprofen using PVP-K30 as a carrier and the tablets prepared from solid dispersion of ketoprofen: PVP-K30 (1:4 ratio) by Solvent evaporation method using different concentrations of superdisintigrant Crospovidone and Citric acid and Sodium bicarbonate in combination (2:3 ratio) varying concentration (1-5%) were used to prepare the tablets. Among all the prepared formulations F5 containing 5% Crospovidone as a superdisintegrant showed highly promising improvement in the dissolution characteristics and thus there is possible enhancement in the Bioavailability of ketoprofen.

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