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Original Article

Formulation and evaluation of fast dissolving tablets of ketoprofen

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ABSTRACT

Ketoprofen is non-steroidal anti-inflammatory drug mainly used for osteoarthritis and rheumatoid arthritis. The major problem with this drug is its very low solubility in biological fluids which results in poor solubility after oral administration. Therefore solid dispersion of Ketoprofen with PEG-6000 and PVP K30 in different weight ratios were prepared with a view to increase it's water solubility. The solid dispersions were evaluated by solubility study, drug content, in-vitro drug release study, dissolution efficiency and characterized by FT-IR. The Ketoprofen SD with PVP K30 (1:3) ratio showed maximum amount of drug release hence it was selected for Fast Dissolving Tablet formulation. The Fast Dissolving Tablets of Ketoprofen were prepared by direct compression technique by addition of different concentrations of superdisintigrants like Sodium starch glycolate, Crosscarmalose sodium and Crospovidone, The prepared tablets were evaluated for Pre-Compression and Post- Compression Parameters among all the formulations F15 showed least disintegration time and % drug release. Stability study of F15 was carried out at 40^0c and 75% RH for three months. Stability study confirms there is no significant change in the formulation of F15.

Keywords: Ketoprofen, Solid dispersion, Direct compression, Fast dissolving Tablets, Superdisintigrants, Stability Study.

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INTRODUCTION

Fast dissolving tablets disintegrate or dissolve quickly in the oral cavity, or swallowed without the need for the administration of water. As the tablet disintegrates in mouth, this enhances the clinical effects of drug through absorption from mouth, pharynx and esophagus 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. Fast disintegrating tablets are also called as mouth-dissolving tablets, melt-in mouth tablets, rapimelts, porous tablets, quick dissolving etc. Recent developments in fast-dissolving tablets (FDT) provide a convenient solution for patients who have difficulties in swallowing conventional solid dosage forms. 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 PEG-6000[12] and PVP[13] as carriers at various proportions (1:1,1:2,&1:3) by using Solvent evaporation technique and the addition of different concentration of superdisintegrants such as sodium starch glycolate[14], crospovidone[15] and Crosscarmalose sodium[16] 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 single punch tablet machine (Cadmach, Ahmedabad).The tablets were evaluated for pre-compression and post-compression parameters. Among all tablet formulations, F15 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 ,Ac-Di-Sol, Sodium Starch Glycolate, Crospovidone, Avicel PH 102. Lactose, Dextrose M/s Healer's Labs Pvt. Ltd., Baddi,Polyvinylglycol-6000 , Methanol LR, Acetone LR, 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, PEG-6000) in proportions, viz. 1:1, 1:2, 1:3 (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 0.45 μm 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 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 Super Disintegrants, the superdisintegrants (Croscarmallose sodium, Sodium starch glycolate and Crospovidone) 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 using a single punch tablet machine (Cadmach, Ahmedabad) to produce convex faced tablets weighing 500 mg each with a diameter of 11 mm.

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. The results were shown in Table 2-3. The tablet thickness was recorded using micrometer (Mityato, Japan).

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.

Hardness [17]**:** Hardness of the tablet of each formulation was determined using Pfizer hardness tester.

Friability[18]**:** 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[19]: 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.

Content uniformity: Ten randomly selected tablets were weighed and powdered in a glass mortar pestle. The weight equivalent to 10 mg Ketoprofen was weighed and dissolved in 5 ml of methanol in volumetric flask using magnetic stirrer, the volume was adjusted to 100 ml with Sorenson's

buffer (pH 6.8) and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml Sorenson's buffer (pH 6.8) in separate volumetric flask. The content in was determined spectrophotometrically at 260 nm.

***In-Vitro* Dissolution Studies**[20-21]**:** *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.

Infrared Spectral Assignment: The pellet of approximately 01 mm diameter of the drug was prepared grinding 3-5 mg of sample with 100-150 mg of Potassium Bromide using hydrostatic press. The sample pellet was mounted in IR compartment and scanned at wavelength 4000 cm^{-1} – 500 cm^{-1}. On analysis of the IR spectra of pure drug (B), no major differences were observed in the characteristic absorption peak (1696, 1655) pattern. The results were shown in Fig: 5,6 and 7.

Stability studies: Stability is defined as "the capacity of the drug product to remain within specifications established to ensure its identity, strength, quality and purity" (FDA 1987). In other words the stability of a drug is its ability to resist detoriation. Stability study of F15 was carried out at 40^{0}c and 75% RH for three months .The tablets were analysed for weight, hardness, friability, *in-vitro* disintegration time, and for drug content at a time interval of one month for the period of three months. The formulation F 15 showed no significant variation in all the parameters under the test period conditions.

RESULT AND DISCUSSION

All the Solid dispersions (SD_S) 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 PEG, PVP-K30, up to 1:3 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[22]. The dissolution parameters of pure drug and SDs are shown in Table: 1. it is indicated that The ketoprofen: PVP-K30.1:3 Solvent evaporation Method has shown maximum dissolution rate. It was converted into Fast Dissolving Formulations with the addition of different concentration of superdisintegrants such as crosscarmalose sodium, sodium starch glycolate, crospovidone. Among all tablet formulations, F15 which contains solid dispersion of ketoprofen and Crospovidone as a superdisintegrant showed least disintegration time and faster dissolution rate than the tablets prepared according to other formulae shown in Fig: 2,3,4. The results of mean hardness, disintegration , The friability, Wt .Variation and Uniformity of dispersion of prepared tablets are shown in Table:2,3.The Best Fit of various kinetics Models for fast dissolving Tablets of Ketoprofen is shown in Table:4. FT-IR spectroscopy was used to study the possible interaction between ketoprofen: PVP-K30 in SDs the spectra showed the characteristic peaks corresponding to the drug and carrier used were unchanged showing no significant interaction between drug and carrier this is shown in Fig: 5,6,7. In order to determine the change in the *in-vitro* release profile on storage stability study of F15 was carried out at 40^{0}c and 75% RH for three months, no visible physical changes were observed in the formulation withdrawn from the humidity chamber.

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 superdisintegrants. 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 and PEG-6000 and were 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-KPVP3 & KPEG1-KPEG3) was found to be from 97.94% to 99.37%,

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 KPVP3 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 three superdisintegrants (croscarmallose sodium, Sodium Starch Glycolate and Crospovidone) were used in different concentrations. The tablets with Crospovidone disintegrate faster then the tablets with the Sodium Starch Glycolate and croscarmalose sodium. The disintegration time of all the formulations were found to be in between 25.68±1.41 sec to134.22±5.16 Sec. The disintegration process of the tablet was fully dependable on nature and concentration of the used superdisintegrant. 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 27.45±1.40 to 125.66±5.76 seconds. The swelling properties of the superdisintegrant were depend 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 followed by croscarmalose sodium and Sodium starch glycolate. The same sequence was observed in case of measurement of dispersion time of the tablet.

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 (1:3 ratio) by Solvent evaporation method using different concentrations of superdisintigrants like Sodium starch glycolate, Crosscarmalose sodium and Crospovidone. Among all the prepared formulations F15 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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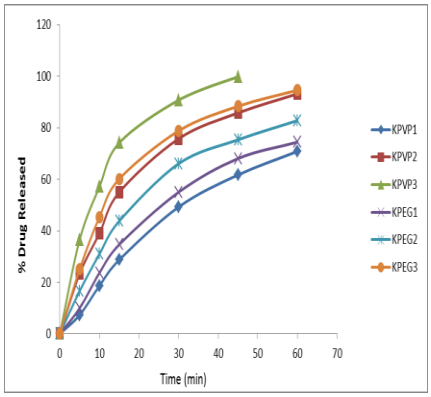

Figure-1: Cumulative Percent Release of Ketoprofen from Solid Dispersions of Ketoprofen-PVP K-30 and Ketoprofen-PEG-6000 Systems

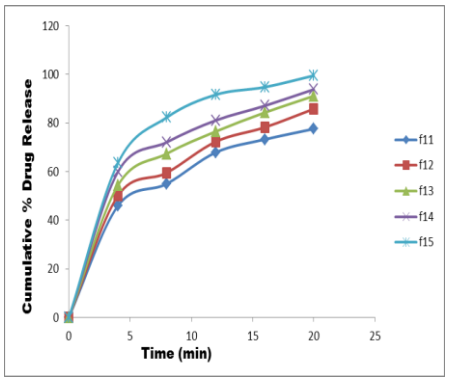

Figure-2: Zero Order Dissolution Release Profile of Ketoprofen from F1-F5

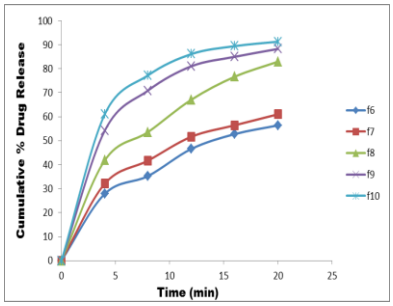

Figure-3: Zero Order Dissolution Release Profile of Ketoprofen from F6-F10

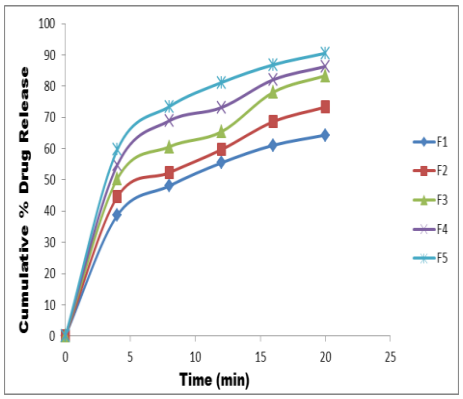

Figure-4: Zero Order Dissolution Release Profile of Ketoprofen from F11-F15

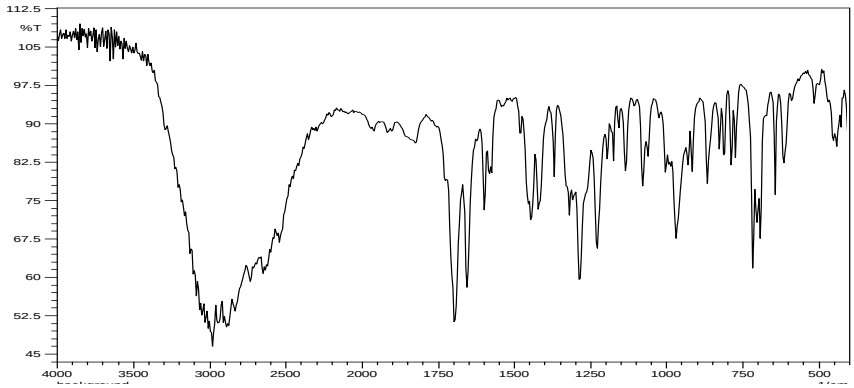

Figure-5: IR Spectra (B) Sample of Ketoprofen

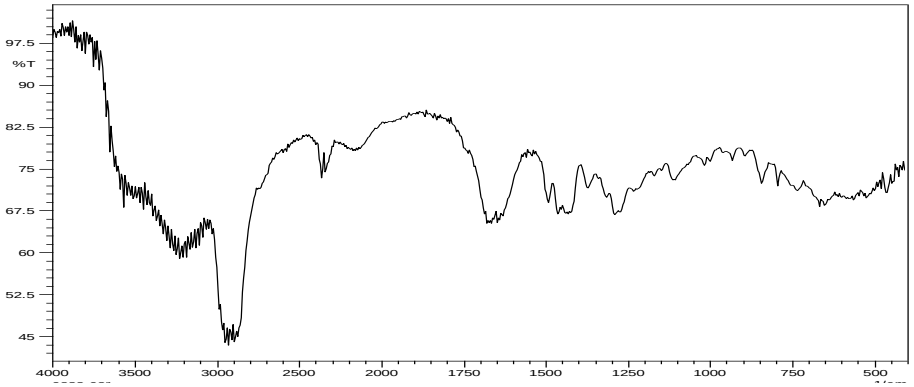

Figure-6: IR Spectra of Crospovidone

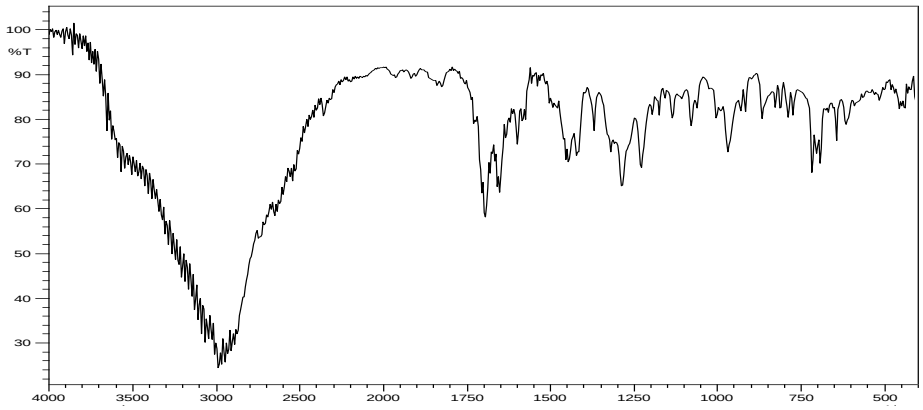

Figure-7: IR Spectra of Mixture of Drug and Crospovidone

Table-1: Dissolution Efficiency of Ketoprofen-PVP K30 &/ Ketoprofen-PEG 6000 Solid Dispersions.

FORMULATION	Dissolution Efficiency (%)	
	DE 15	DE 30
Pure drug	2.90	6.48
KPVP1	12.92	25.80
KPVP2	30.10	47.90
KPVP3	44.12	63.30
KPEG1	17.54	31.60
KPEG2	23.22	39.12
KPEG3	34.18	52.10

Table-2: Characterization of Fast Dissolving Tablets.

Formulation	Thickness (mm)	Weight (mg)	Friability (%)	Hardness (Kg/cm^2)
F1	6.325±0.014	500.68 ±1.50	0.478 ±0.02	3.16 ±0.05
F2	6.342±0.026	496.64 ±3.72	0.440 ±0.04	3.13 ±0.03
F3	6.343±0.034	497.30 ±0.58	0.639 ±0.06	2.80 ±0.1
F4	6.325±0.004	501.32 ±2.08	0.781 ±0.04	2.82 ±0.1
F5	6.349±0.037	496.64 ±1.54	0.870 ±0.06	2.73 ±0.12
F6	6.342±0.029	502.68 ±1.54	0.719 ±0.06	3.0 ±0.173
F7	6.348±0.043	500.32 ±1.50	0.519 ±0.04	3.66 ±0.1
F8	6.349±0.021	500.30 ±2.32	0.800 ±0.01	3.22 ±0.10
F9	6.334±0.034	499.36 ±1.54	0.638 ±0.03	3.20 ±0.06
F10	6.325±0.008	498.66 ±2.08	0.519 ±0.02	3.50 ±0.12
F11	6.345±0.016	499.34 ±3.22	0.519 ±0.04	3.42 ±0.12
F12	6.372±0.031	498.68 ±0.52	0.719 ±0.06	3.13 ±0.12
F13	6.346±0.034	501.66 ±2.10	0.760 ±0.06	3.16 ±0.14
F14	6.335±0.031	499.30 ±1.54	0.519 ±0.02	3.06 ±0.20
F15	6.348±0.031	501.32 ±1.52	0.478 ±0.06	3.3 ±0.2

Table-3: Characterization of Fast Dissolving Tablets.

Formulation	Disintegration time (Seconds)	Wetting time (Seconds)	Dispersion time (Seconds)
F1	95.53 ±1.50	87.38 ±1.72	114.30 ±3.38
F2	86.50 ±2.36	80.12 ±3.92	101.42 ±2.40
F3	70.25 ±3.76	65.34 ±3.66	84.78 ±4.26
F4	60.58 ±1.86	55.04 ±3.12	71.80 ±3.40
F5	51.94 ±3.34	49.22 ±3.50	64.68 ±4.22
F6	134.22 ±5.16	125.66 ±5.76	142.72 ±4.82
F7	119.93 ±4.96	110.22 ±3.54	124.90 ±4.62
F8	59.48 ±1.50	80.08 ±4.40	86.22 ±2.72
F9	45.11 ±2.14	62.69 ±2.50	69.71 ±1.60
F10	35.60 ±1.48	48.98 ±3.46	55.10 ±3.12
F11	47.48 ±1.80	60.04 ±3.82	67.44 ±2.52
F12	36.02 ±1.60	42.94 ±3.04	54.35 ±2.64
F13	29.02 ±1.70	31.83 ±2.84	42.78 ±1.12
F14	27.71 ±1.14	29.67 ±1.46	33.68 ±2.08
F15	25.68 ±1.42	27.44 ±1.40	30.91 ±1.68

***n=3**

Table-4:Various kinetics Models of fast dissolving Tablets of Ketoprofen

Formulatio Code	Zero order				First order				
	Intercept	R2	Slope	K (mg/mi)	Intercept	R2	Slope	K (min^{-1})	t1/2
F1	16.29	0.797	2.831	6.519793	1.922	0.9	0.02	0.04606	15.04559
F2	17.88	0.808	3.187	7.339661	1.921	0.935	0.026	0.059878	11.57353
F3	20.23	0.806	3.606	8.304618	1.923	0.955	0.035	0.080605	8.597482
F4	23.89	0.757	3.697	8.514191	1.892	0.944	0.04	0.09212	7.522796
F5	26.56	0.734	3.872	8.917216	1.881	0.956	0.048	0.110544	6.268997
F6	10.19	0.891	2.628	6.052284	1.957	0.952	0.017	0.039151	17.7007
F7	12.76	0.856	2.771	6.381613	1.945	0.938	0.019	0.043757	15.83747
F8	15.63	0.883	3.805	8.762915	1.962	0.99	0.037	0.085211	8.132753
F9	24.39	0.76	3.884	8.944852	1.889	0.946	0.044	0.101332	6.838906
F10	28.2	0.711	3.932	9.055396	1.856	0.93	0.051	0.117453	5.900232
F11	18.78	0.812	3.45	7.94535	1.919	0.946	0.03	0.06909	10.0304
F12	20.05	0.821	3.76	8.65928	1.932	0.974	0.039	0.089817	7.715689
F13	22.67	0.8	3.962	9.124486	1.933	0.978	0.048	0.110544	6.268997
F14	25.69	0.761	3.998	9.207394	1.92	0.973	0.055	0.126665	5.471125
F15	29.06	0.761	4.291	9.882173	1.993	0.972	0.091	0.209573	3.306724

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