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STUDIES ON DESIGN AND DEVELOPMENT OF POORLY WATER SOLUBLE NSAID DRUG BY ORAL DRUG DELIVERY SYSTEM

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Abstract

The poor water solubility is the main reason for poor oral bioavailability and it causes research and development more difficult. There are different methods for the improvement of solubility such as amorphization, crystal modification, micronization, self-emulsification, cyclodextrin complexation, and pH modification. There is various difficulty of improvement of water solubility of poor water-soluble drug according to different routes of administration. An estimated 40% of approved drugs and nearly 90% of the developmental pipeline drugs consist of poorly soluble molecules. Several marketed drugs suffer from poor solubility, low permeability, rapid metabolism and elimination from the body along with poor safety and tolerability. Poor aqueous solubility, and consequently also poor dissolution rate, is a major challenge specifically in the systemic delivery of orally administered BCS class II and IV drugs. A better knowledge of biopharmaceutical and physiochemical property of drug and their limitation helpful for efficient formulation development for poorly water-soluble drugs. The article describes studies on design and development of poorly water soluble NSAID drug by oral drug delivery system

Key words: Bioavailability, Crystal modification, Dissolution, Electrospinning, Solubility.

Introduction

The search for innovative medicines in disease management without compromising on safety and efficacy is a challenge. In spite of significant success in the discovery of new drugs, there are still unmet medical conditions which need effective therapy. Market potential, competition among companies, dry pipeline of developmental candidates of various companies have hastened the drug discovery and development process. As a result, a significant number of drugs getting approvals have poor biopharmaceutical properties. An estimated 40% of approved drugs and nearly 90% of the developmental pipeline drugs consist of poorly soluble molecules. Several marketed drugs suffer from poor solubility, low permeability, rapid metabolism and elimination from the body along with poor safety and tolerability [2]. Poor aqueous solubility, and consequently also poor dissolution rate, is a major challenge specifically in the systemic delivery of orally administered BCS class II and IV drugs. Physico-chemical techniques that have been employed to improve the solubility of these drugs include formation of pro-drugs, formation of salts, co-precipitation, solvent evaporation and size reduction (or micronisation). Formulation strategies that have been investigated for the same purpose include melt extrusion/granulation, formation of solid dispersions and formation of

inclusion complexes [7].

Fig. no 1: Insoluble Drug Delivery Strategies

Furthermore, excipients such as surfactants, polymers, super-disintegrants and multifunctional fillers have been included in dosage forms to increase the apparent solubility of drugs. Ketoprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory agent (NSAIA) with analgesic and antipyretic properties. By using HPMC along with sodium CMC as exicipient the tablet formulation is done by Wet Granulation Method [4].

Over the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing1. Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of already used drug molecule by formulating a convenient dosage forms for administration and to achieve better patient compliance. To develop a chemical entity, a lot of money, hard work and time are required. So focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects [5].

Material and Method:

Characterization of Drug Melting behavior

Melting point of KET was determined using automated melting point apparatus OptiMelt (SRS).

UV spectroscopy

A UV spectrum of KET was recorded in MeOH using 'Spectrum Measurement' function of UV-Visible Spectrophotometer (Jasco).

Vibrational spectroscopic study

After starting the instrument, 'Background Measurement' was performed without placing the drug on panel. For 'Sample Measurement', pure KET was placed on cleaned panel of FT-IR Spectrometer (Bruker). The placed KET was sandwiched between panel and upper arm. This sample was scanned over a wave number range of 4000 to 500 cm^{-1}

Solubilizing agent

Solubilizing materials like super disintegrants such as crospovidone used as solubilizing agents in formulation which increase the solubility and dissolution rate of poorly water soluble drugs. The superdisintegrants acts as hydrophilic carrier for poorly water soluble drug. It is used for dissolution enhancement of poorly soluble drug.

Construction of calibration curve for KET General

For preparing various solutions of drug, suitable quantity of KET was weighed on aluminum foil using pre-calibrated analytical weighing balance. The weighed quantity was transferred to volumetric flask and solubilized using analytical grade MeOH. Prior to analysis, both cuvettes were washed with distilled water twice and rinsed with MeOH twice to ensure complete cleaning. During UV analysis, both cuvettes were filled with MeOH and reading was adjusted using 'Auto Zero' button. Then, subsequent UV absorbance measurements were carried out.

Preparation of Stock Solution

50 mg of Ketoprofen was weighed accurately and dissolved in 5 ml of methanol in a 100 ml of volumetric flask and volume was made up to 100 ml with the Sorenson's buffer (pH 6.8). 10 ml of this solution was diluted with 100 ml Sorenson's buffer (pH 6.8) to obtain a stock solution of 50 mg From this stock solution.

Determination of Analytical Wavelength (λ_{max})

Sufficient volume of Stock-1 was scanned under UV region of 400-200 nm using MeOH as blank. The wavelength, at which there was maximum absorption, was selected as wavelength foranalysis.

Preparation of Standard curve

50 mg of Ketoprofen was weighed accurately and dissolved in 5 ml of methanol in a 100 ml of volumetric flask and volume was made up to 100 ml with the Sorenson's buffer (pH 6.8). 10 mLof this solution was diluted with 100 ml Sorenson's buffer (pH 6.8) to obtain a stock solution of 50 mg From this stock solution. aliquots of 1 ml, 2 ml, 3 ml, 4 ml and 5 ml were taken and transferred to 10 ml volumetric flask and volume was made up to 10 ml with Sorenson's buffer (pH 6.8). The absorbance of these solutions was measured at 260 nm against a blank Sorenson's buffer (pH 6.8).

Preparation of Preliminary Batches of tablets

The preliminary batches of Tablets were tried on the basis of previous reports. These batches were studied for their *in vitro*. These batches were prepared and evaluated for optimizing the formulation on the basis of parameter like hardness, Dispersion time, Disintegration time, friability.

Table No. 1: Formulation and Process Variables & Level

Sr. No.	Independent variables	Units	Levels	
			Low	High
1	Starch concentration	mg	25	75
2	HPMC concentration	mg	100	200
3	Sodium Alginate	mg	75	125

Table No. 2: Different Formulation

Material	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ketoprofen	200	200	200	200	200	200	200	200	200	200	200	200
Talc	20	20	20	20	20	20	20	20	20	20	20	20
MCC	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Starch	50	50	75	50	75	25	50	50	50	85.36	14.64	25
Crospovidone	20	20	20	20	20	20	20	20	20	20	20	20
HPMC	150	220.71	200	150	100	200	150	150	79.29	200	200	200
Sodium alginate	64.64	100	75	100	125	125	100	135.36	100	100	100	75
Sum	511.64	617.71	597	547	547	597	547	582.36	476.29	632.36	561.6	547

Method of preparation of Tablets:

Preformulation studies:

Differential scanning calorimetry:

The DSC curves of Ketoprofen, HPMC K4M, Sodium alginate and physical mixture of Ketoprofen were obtained using differential scanning calorimeter at increasing heating rate at 10˚ C/min and heated over a temperature range of 50˚ C to 250˚ C in an atmosphere of nitrogen (20ml/min). Accurately twelve mg of sample was taken in a hermetically sealed, flat bottom aluminum sealed pan and placed at sample stage and thermograms were recorded.

Fourier Transforms Infrared Spectroscopy:

FT-IR spectra of Ketoprofen, HPMC K4M, Sodium alginate and physical mixture of Ketoprofen were recorded at room temperature condition using KBr pellet technique. KBr pellets were prepared by applying a pressure of 5-7 tons. IR spectrum was measured at the maximum at 4000 cm-1 using methanol as a blank. Following steps were followed for preparation of tablets

a) **Weighing of drug and Excipient:** Drug and excipient were accurately weighed on aluminum foil using pre-calibrated analytical balance.

b) Compression was done using HPMC K4M and Sodium alginate as a carrier. HPMC K4M and Sodium alginate were included in the formulations in various proportions after sieving (sieve no 60) separately and mixed with Ketoprofen (sieve no. 100).

c) **Granulation:** The powders were blended and granulated with 10% w/v starch paste. The obtained wet mass was pass through sieve number 16 (mesh size: 1000 µm) and the granules were dried at 50º C for2h.

d) **Adding Lubricant:** The dried granules were pass through sieve no. 25 (mesh size: 650 µm) and were lubricated with mixture of talk and magnesium stearate in definite proportion.

e) **Compressed**: The lubricated granules were compressed into final dosage form(Tablet).

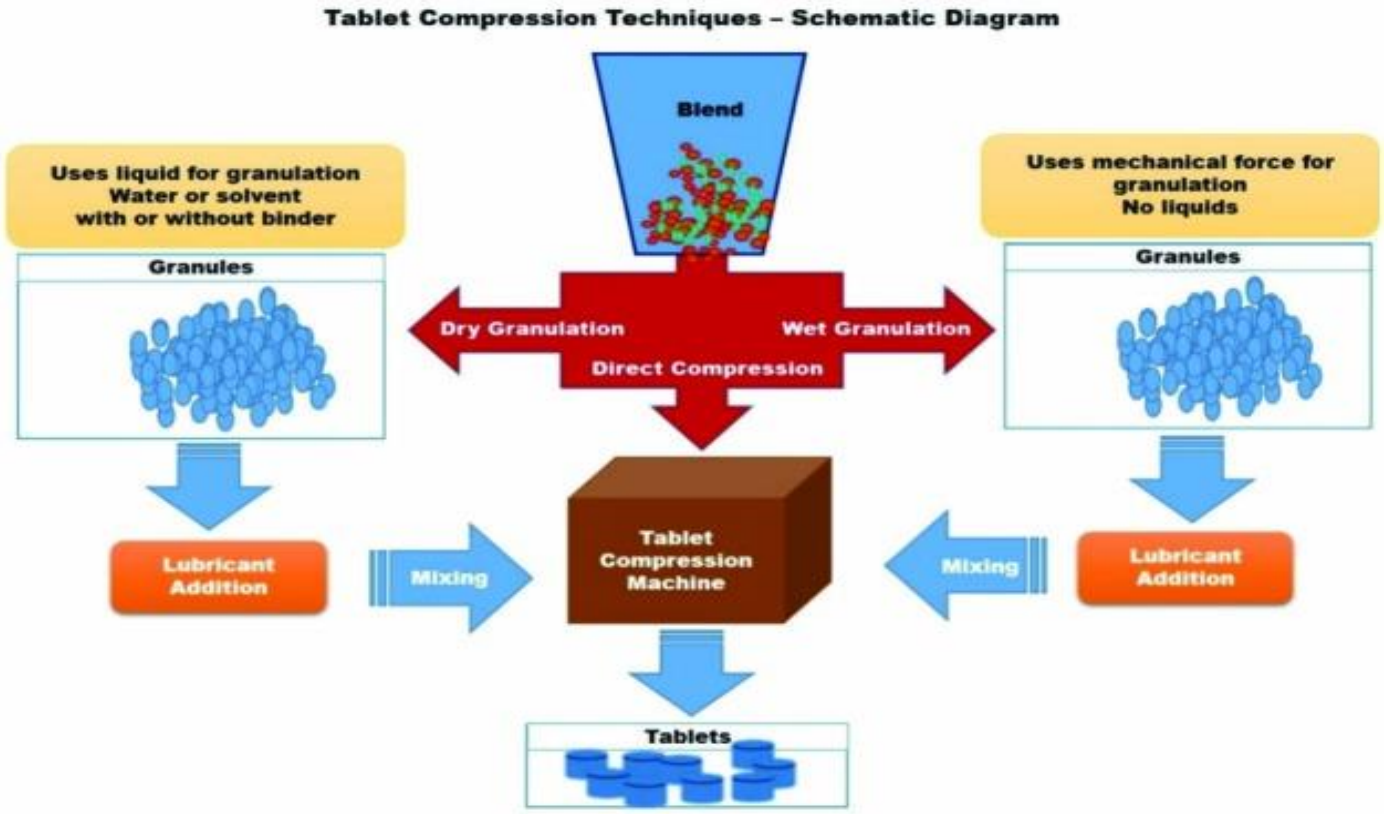

Fig. No 2: Tablet Compression Technique

f. Storage: The dry patches were kept into self-sealing polythene bags, These bags we stored in desiccators until use.

Evaluation

A. Evaluation of Tablets:

a. Physicochemical evaluation
b. In vitro evaluation

B. Physicochemical evaluation

1. Thickness and hardness:

Prepared matrix tablets were evaluated for thickness by using vernier calipers. Hardness of the tablets was evaluated using Monsanto hardness tester, which is expressed in kg/cm2.

2. Friability:

Friability of tablets was determined using Roche friabilator. Twenty tablets were weighed and placed in a chamber. The friabilator was operated at 25 rpm for four minutes (per 100 revolutions) and the tablets were subjected and the tablets were subjected for combined effect of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets were then dusted and reweighed and the percentage of friability was calculated by using the following formula,

$F = Wi - Wf / Wi \times 100$

3. Weight variation:

Weight variation test was performed according to USP 2004, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The percentage deviation was calculated and checked for weight variation.

4. Swelling index:

The swelling index of the tablets was performed, to comprehend the influence of swelling and erosion behavior of the formulation on its drug release, according to the procedure described below. The tablet was weighed accurately (W0) and placed in a Petri dish of height 1.6 cm and diameter of about 9 cm containing 10 ml of distilled water at room temperature (27 0C±1) and the tablet was covered fully with water. At the end of 2 hours, the tablets were removed from the Petri dish and excess surface water was removed carefully using filter paper and swollen tablets were reweighed (Wt). The swelling index was calculated according to the formula;

swelling index= (Wt-W0)/W0*100

Where,

Wt is the weight of Tablet at time‘t’,

W0 is the weight of Tablet at time t = 0.

5. Drug content:

Ten tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 200 mg for Ketoprofen was transferred in to a 100 ml volumetric flask and extracted with 0.1N hydrochloric acid and kept aside for 2 hours. Then the solutions were filtered, suitable dilutions were made and absorbance was measured by using SHIMADZU UV- Visible spectrophotometer at 262 nm. Drug content was calculated.

6. In vitro drug release studies:

The release studies of all the matrix tablets were performed using a USP type I dissolution test apparatus (paddle apparatus, 100 rpm, 37 ± 0.5ºC) in 900 mL of dissolution medium (SGF). 5 ml samples were withdrawn with pipetting syringe at appropriate time intervals and filtered through whatmann filter paper. Samples were estimated for drug using UV spectrophotometer at suitable wave length 262 nm. Sink conditions were adjusted with the addition of an equal volume of fresh dissolution medium at the same temperature throughout the test. The pH of the dissolution medium was kept 1.2 for 2h then, pH of the dissolution medium was adjusted to 7.4 was kept for 3h, pH of the dissolution medium was adjusted to 6.8 and maintained up to 24h

B. Evaluation of granules

1. Determination of bulk density and tapped density:

An accurately weighed quantity of the granules (W), was carefully poured into the graduated cylinder and the volume (V0) was measured. Then the graduated cylinder was closed with lid, set into the density determination apparatus. The density apparatus was set for 100 taps and after that, the volume (Vf) was measured and continued operation till the two consecutive readings were equal. The bulk density, and tapped density were calculated using the formulae.

Bulk density = W/V0 Tapped density = W/Vf

2. Compressibility index:

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index % = (V0 - Vf) / V0 × 100

3. Hausner's ratio:

Hausner's ratio was measured by the ratio of tapped density to bulk density.

Hausner's ratio = Tapped density/ Bulk density

4. Angle of repose:

Angle of repose was determined using funnel method. The height of the funnel was adjusted in such a way that the tip of funnel just touches the heap of the blends. Accurately weighed blends are allowed to pass through the funnel freely on to the surface. The height and diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan\theta = h / r$

Where, θ = Angle of repose,

h = height of the pile,

r = radius of plane surface occupy by the powder

Evaluation of Optimized Batch

From the above eight prepared batches of Tablets batch F10 showing the good results so, this batch will be considered as optimized batch. This batch was re-formulated with more accuracy and precision. Which will ultimately, gives the better results as compared with previous F10. Characterization of Drug Melting Behavior

The melting range of KTE was found to be 90 to 97˚C.

Vibrational spectroscopic study

FTIR spectrum of ketoprofen was recorded and characteristic peaks were observed at 1693.50, 1723 and 2980.02 cm-1 due to Ketonic C=O stretching, Acidic C=O stretching and -OH (-COOH) respectively.

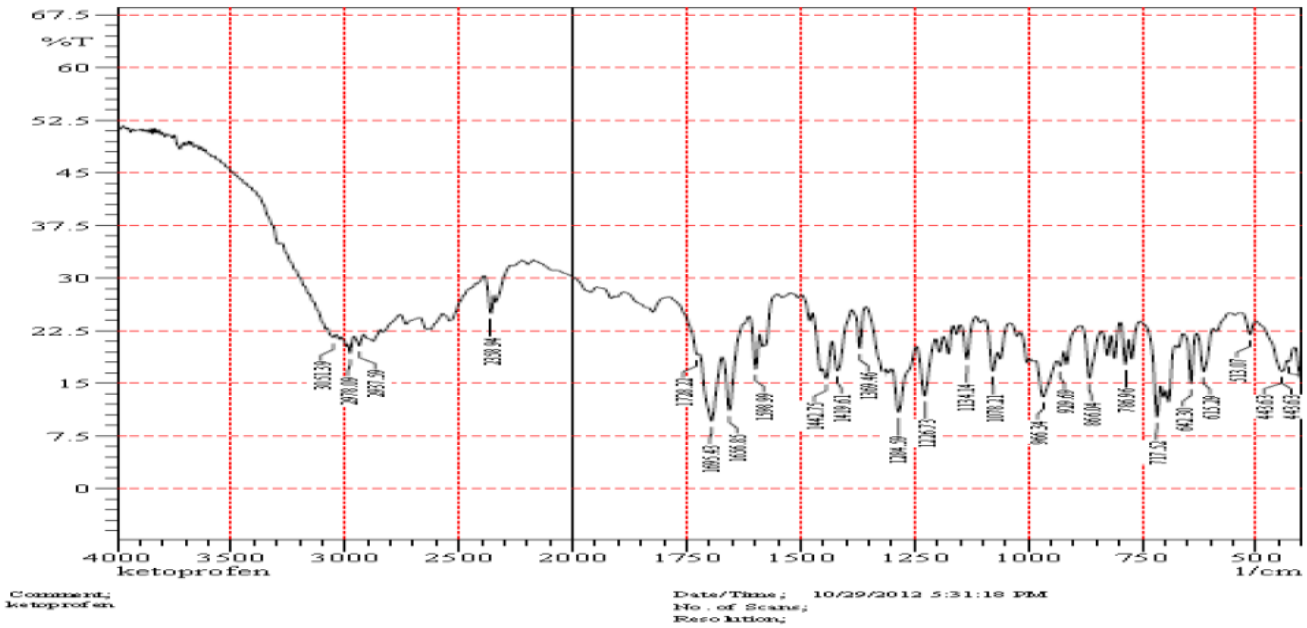

Fig No 3: FT-IR Spectrum of KTE with Structure

Table No:3: Assignments for the Principle FT-IR Absorbance Bands of KTE

Sr. No.	Peak Maximum (cm^{-1})	Assignment
1	701.75	C-H, Phenyl ring substitution
2	757.78	C-H, Phenyl ring substitution
3	1048.34	C-O Stretch
4	1090.25	C-O Stretch
5	2980.02	Acidic C=O stretching
6	1452.58	C-H Bending
7	1693.50	Ketonic C=O stretching
8	3336.42	O-H Stretch

Construction of calibration curve for KTE

λ_{max} for KTE was found to be 256 nm. The standard calibration curve of IBU was obtained by plotting the absorbance of the standard solution against its concentration at 256 nm. The standard solution of KTE showed the linear curve with correlation coefficient of 0.997. Their equations of lines was y = 0.0986x + 0.004 at selected λ_{max}. Following table shows absorbance of respective standard solution. The standard curve for KTE at 256 nm is shown in Fig. 4.

Table No. 4: Calibration Range for KTE

Sr No.	Concentration(µg/ml)	Absorbance
1	1	0.0962
2	2	0.1934
3	3	0.2984
4	4	0.4218
5	6	0.5988
6	8	0.7824

Although a pre-validated UV method was used for the analysis, λ_{max} for KTE was confirmed by scanning standard solution of KTE. λ_{max} was found to be 256 nm. The calibration curve was developed in the concentration range of 01-10 µg/mL. The solvent used for the calibration curve development was MeOH. The method was found to be linear (R^2 =0.997). R^2 near 1 gave the confidence that standard solutions of KTE follow the Beer-Lambert Law.

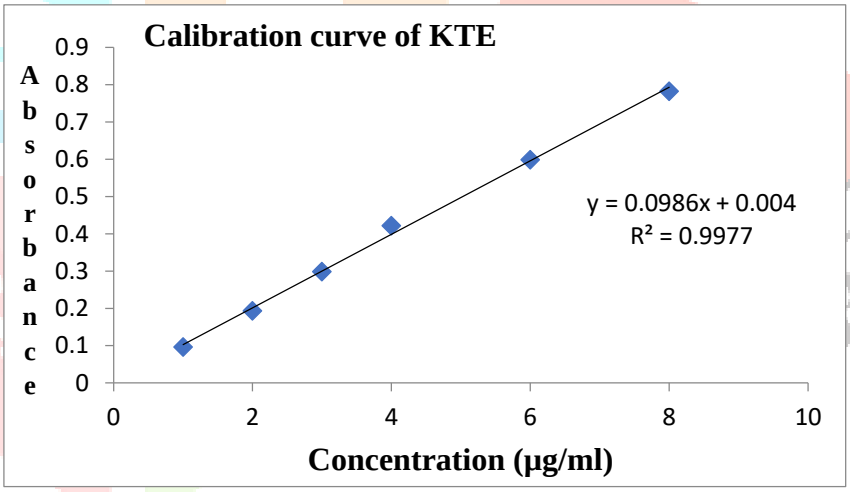

Fig No 4: Standard Curve for KTE

Differential Scanning Colorimetry (DSC):

In the DSC plot of KTE the sharp curve was observed at 110°C showed the melting of the KTE which is match with the melting point (94 °C) given in the previous reports. From the DSC thermo gram it was observed that the all the compound showed the melting curve in the specific range which are standard range of compound.

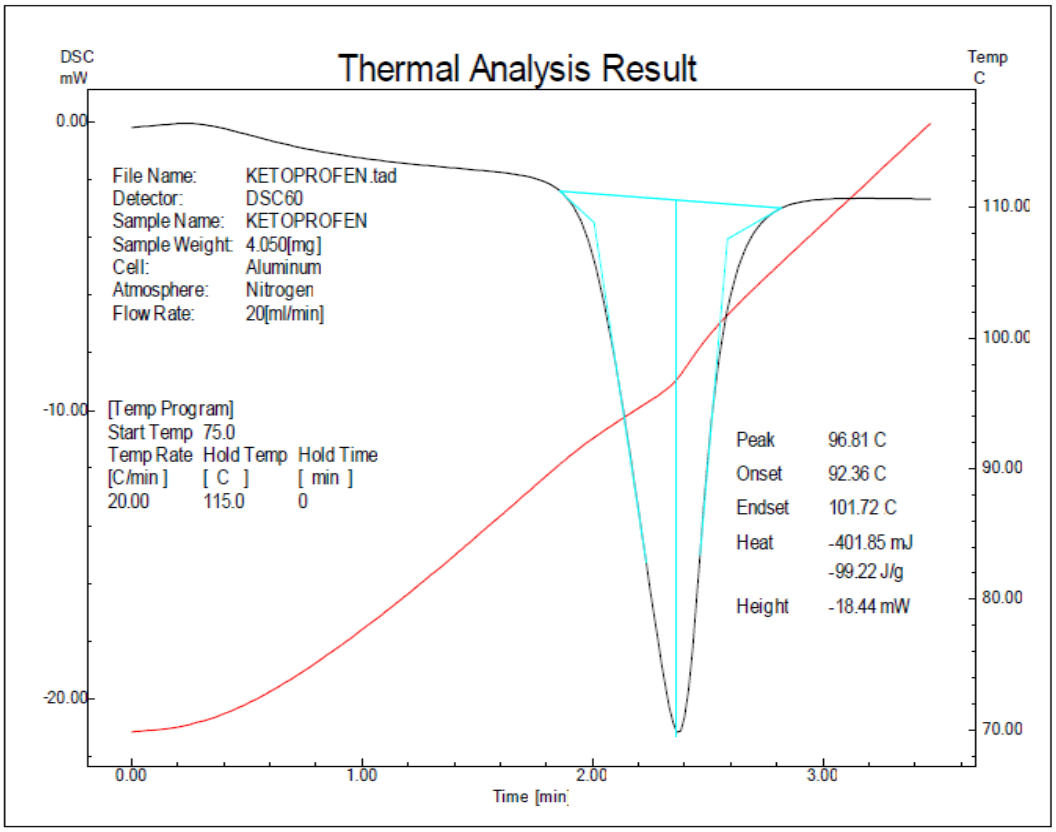

Fig No 5: Differential Scanning Colorimetry (DSC)

Evaluation Test

Characterization of Blend of API and Excipients:

The blend of API and excipients was evaluated for parameters like Angle of repose, Bulk density, Tapped density, Compressibility index and Hausner's ratio. The results obtained were as shown in Table 3.

Table. No 5: Angle of Repose, Bulk density, Tapped Density and Compressibility Index for the Formulations of Ketoprofen Matrix Tablets containing HPMC K4M, Starch & Sodium Alginate in different concentrations

Sr.No	Batches	Angle of Repose	Bulk density	Tapped density	compressibility Index
1	F1	25.29	0.526	0.632	15.77
2	F2	26.24	0.497	0.584	14.89
3	F3	26.85	0.481	0.556	13.48
4	F4	27.54	0.421	0.476	11.55
5	F5	29.53	0.449	0.504	10.91
6	F6	24.98	0.479	0.558	14.16
7	F7	25.68	0.498	0.596	16.10
8	F8	26.54	0.448	0.512	12.50
9	F9	27.42	0.492	0.570	15.33
10	F0	28.45	0.450	0.510	11.02
11	F11	29.49	0.498	0.586	16.08
12	F12	24.26	0.479	0.557	14.2

Water uptake study (% Swelling)

A direct correlation between Swelling Index and Lag Time was observed from the obtained results. The lag time was found to be increased with increasing swelling index. Higher Swelling Indices were observed in formulation batches containing higher amount of HPMC K4M. This may be due to uptake of water and swelling of the polymer which is hydrophilic and forms a gel upon hydration.

Table No. 6 : Swelling

Batch code	Swelling(%)
F1	60.52
F2	68.42
F3	66.25
F4	59.46
F5	43.52
F6	65.75
F7	58.96
F8	61.42
F9	38.53
F10	65.51
F11	64.56
F12	67.25

Thickness, Hardness and Weight variation, Friability:

Table No 7: Thickness, Hardness and Weight variation, Friability for the formulations of Ketoprofen Matrix tablets containing HPMC K4M, Starch & and Sodium Alginate in different concentrations

Sr. No	Batches	Thickness	Hardness	Weight variation	Friability
1	F1	2.1± 0.02	4.8 ± 0.12	504±1.2	0.63
2	F2	2.2± 0.01	4.6 ± 0.14	519±1.6	0.34
3	F3	2.1± 0.02	4.7± 0.17	512±1.8	0.26
4	F4	2.1± 0.01	4.2 ± 0.12	515±1.2	0.29
5	F5	2.2± 0.02	4.0 ± 0.21	514±2.1	0.46
6	F6	2.1± 0.01	4.2 ± 0.08	518±2.2	0.53
7	F7	2.1± 0.02	4.7 ± 0.16	516±2.1	0.34
8	F8	2.2± 0.01	4.9 ± 0.12	514±2.4	0.54
9	F9	2.1± 0.02	4.8 ± 0.14	521±1.3	0.32
10	F0	2.2± 0.02	4.1 ± 0.21	514±2.3	0.45
11	F11	2.1± 0.01	4.3 ± 0.08	518±2.2	0.38
12	F12	2.1± 0.02	4.6 ± 0.16	517±1.4	0.46

Drug content:

The % drug content of prepared patches is shown in following table.

Table No 8: Drug content for the Formulations of Ketoprofen Matrix Tablets containing HPMC K4M, Starch and Sodium Alginate in different concentrations

Sr. No	Batches	Drug content%
1	F1	97.24
2	F2	94.56
3	F3	89.87
4	F4	78.95
5	F5	92.85
6	F6	93.65
7	F7	97.56
8	F8	85.62
9	F9	92.75
10	F0	98.88
11	F11	86.69
12	F12	93.18

***In vitro* dissolution studies**

Table No. 13 shows % drug release for all batches and the release pattern for each batch using Sorenson's buffer
Table No. 13: % Release of KTE from Tablets.

Table No. 9: Shows % Drug Release

Sr. No.	Batch code	% Cumulative release
1	F1	75.26
2	F2	64.53
3	F3	68.98
4	F4	74.47
5	F5	79.81
6	F6	69.83
7	F7	74.54
8	F8	75.11
9	F9	92.45
10	F10	69.16
11	F11	68.92
12	F12	67.46

Table No: 10. Release Pattern of KTE from Tablet in *in vitro* Dissolution Studies F1-F6

Time (hrs.)	0	2	4	6	8	10	12
F1	0	13.99	23.84	38.21	51.46	68.48	75.26
F2	0	7.16	15.42	32.51	42.53	56.24	64.53
F3	0	8.16	16.57	31.64	46.71	59.76	68.98
F4	0	12.68	24.58	37.95	52.43	70.14	74.47
F5	0	15.42	24.56	39.48	53.42	71.38	79.81
F6	0	8.19	16.87	31.92	43.21	57.48	69.83

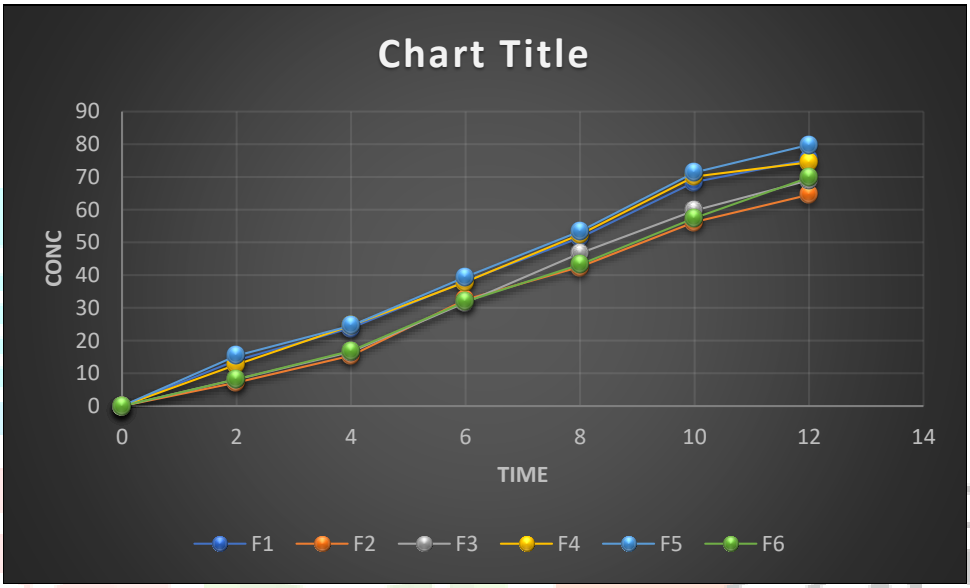

Fig No 6: Release Pattern of KTE from Tablet in *in vitro* Dissolution Studies F7-F12

Time (hrs.)	0	2	4	6	8	10	12
F7	0	13.42	23.11	36.89	50.42	67.91	74.54
F8	0	13.63	24.53	38.46	50.12	68.62	75.11
F9	0	20.12	35.12	46.97	67.23	78.42	92.45
F10	0	8.13	16.42	30.56	46.82	58.96	69.16
F11	0	7.96	15.68	28.96	45.62	57.43	68.92
F12	0	7.98	14.35	27.68	45.23	56.65	67.46

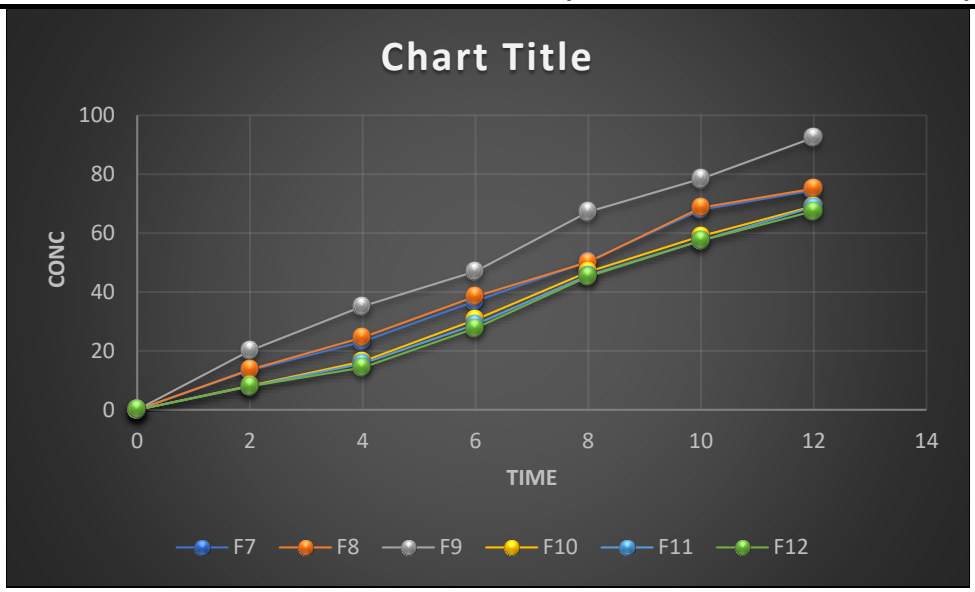

Fig No 7: Release Pattern of KTE from Tablet in *in vitro* Dissolution Studies.

Optimization of formula:

Optimization of variables by using Box- Bhenken design

The mathematical model describing percent drug release and total drug content of KTE tablets as functions of the coded independent variables in the selected ranges was demonstrated by the following second order polynomial equations.

Percent drug release: $14.79-14.20*A+1.27*B+1.54*C-0.6950*AB-0.3400*AC+1.54*BC+4.76*A^2-75.87*B^2-13.88*C^2$

Total drug content: $+76.22-11.31*A-0.0225*B+1.12*C$

The significance of each coefficient was determined using p-value, which is used as a tool to check the interaction strength between each independent variable. When a factor and an interaction among variables have a p- value less than 0.05, they influence the process in a significant way for a confidence level of 95%. The significance of the F- value depends on the number of degrees of freedom (DF) in the model and is shown in the p-value column (95% confidence level). In general, the effects lower than 0.05 are significant. The analysis of variance Table No: 27 showed that this regression model was highly significant ($p < 0.01$) with F- values of 33.18 and 34.302 for percent drug release and total drug content respectively. The F- values of 0.4907 and 1.54 for lack of fit implies that they are not significant comparing to the pure error.

Table No: 11. Analysis of Variance for Response Surface Cubic Model of Total Drug Content determined by Box-Behnken Design

	Sum of squares	df	Mean square	F-value	P-value	Significant
Model	10.33	3	344.64	33.18	0.0001	
A-HPMC	10.23	1	1023.78	98.57	0.0001	
B-Starch	0.0041	1	0.0041	0.0004	0.9846	
C-Sdium alginate	10.12	1	10.12	0.9749	0.3447	
Residual	114.25	11	10.39			
Lack of Fit	78.64	9	8.37	0.4907	0.8138	Not significant
Pure Error	35.61	2	17.34			

Cor Total	1148.64	14				

RSM graphs for percent drug release of KTE

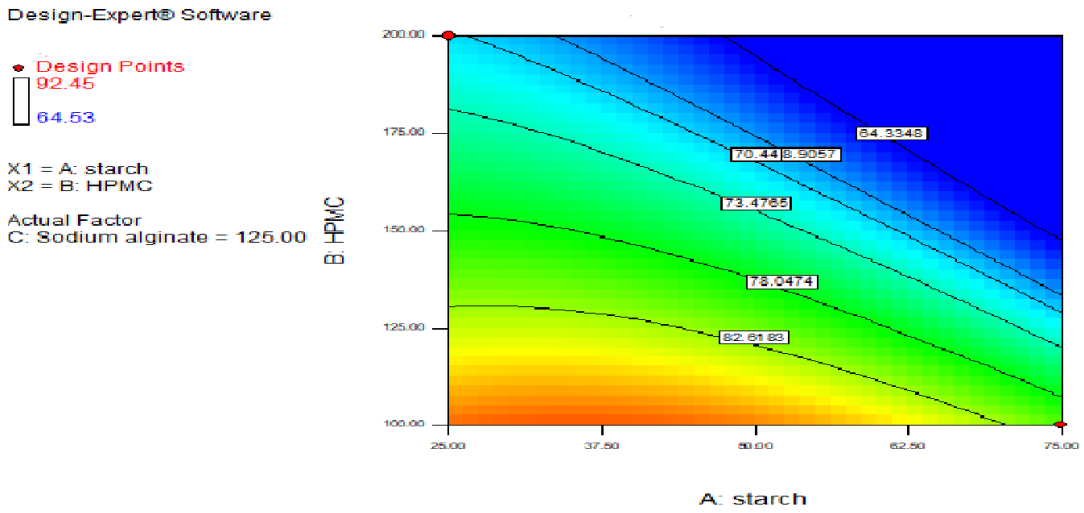

Fig No 8: Effect of HPMC and Starch Concentration on Drug Release

This response plot shows the effect of HPMC and Starch concentration on drug release. When the polymer concentration in the formulation increased, drug release decreased.

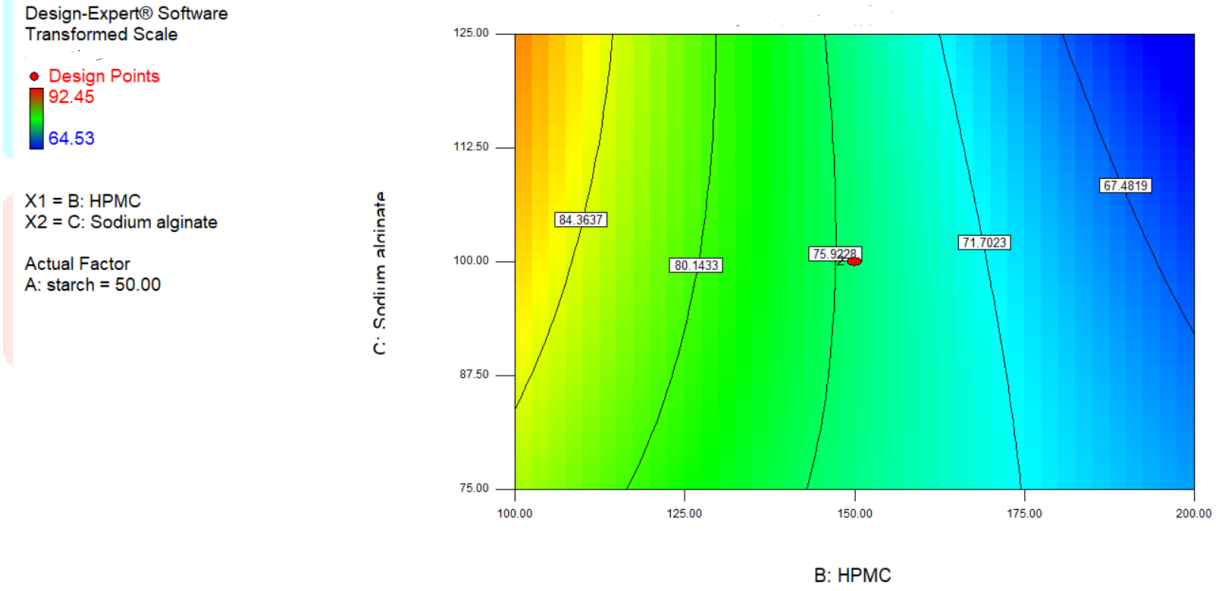

Fig No 9: Effect of HPMC and Sodium Alginate Concentration on Drug Release

This response plot shows the effect of HPMC and Sodium Alginate concentration on drug release. The polymer is used in the sustained release due to its viscosity which plays a major role in the sustained release behavior of the tablet. In RSM plot when the polymer concentration is high, the release the drug will be low.

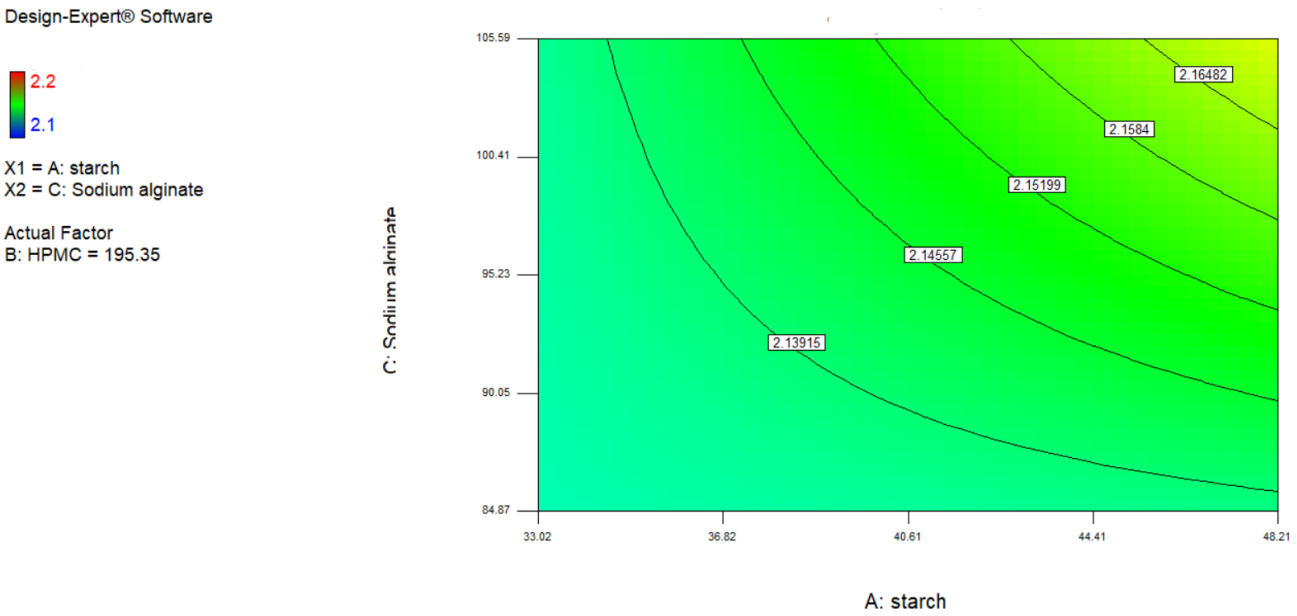

Fig No 10: Effect of Starch and Sodium Alginate Concentration on Drug Release

This response plot shows the effect of Starch concentration and Sodium alginate concentration on drug release. The double effect of the binder and wetting agent on the release profile was observed. If we increase Starch and Sodium alginate concentration it leads to slightly increase in drug release.

Table No: 12. Post Compression Parameters of KTE Tablet

F10.-OB	
Time (hrs.)	**Optimized batch**
0	0± 0.0
2	8.24
4	16.83
6	30.48
8	46.80
10	57.11
12	68.32

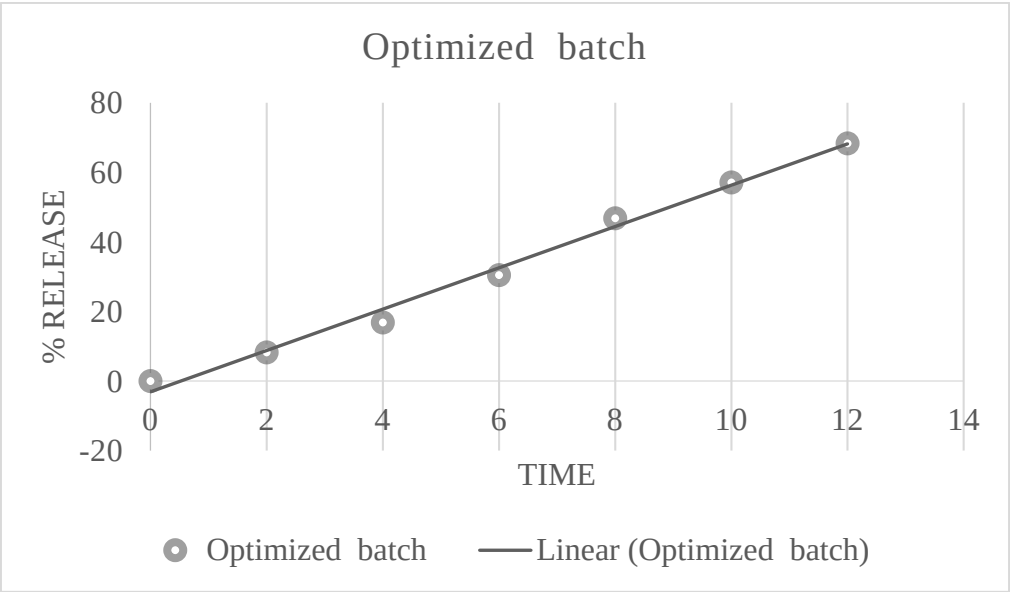

Fig No 11: Dissolution Profile of Batch F10-OB

From the experimental design the software (design expert) gives the predicted batches having a good composition of the HPMC, Starch, Sodium alginate etc. from these the optimized batch was selected (Batch-OB).

Evaluation of Optimized Batch

From the above eight prepared batches of Tablets batch F10 showing the good results so, this batch will be considered as optimized batch. This batch was re-formulated withmore accuracy and precision. Which will ultimately, gives the better results as compared with previous F10.

Batch F10 is OB which was re- formulated with precise manner. The results of evaluation of optimized batch (OB) are shown in following table.

Table No. 13: Results for Optimized Batch

Sr. No.	Evaluation Test	Result
1	Drug release	68.32%
2	Thickness	2.1± 0.02
3	Hardness	4.8 ± 0.14
4	Weight variation	521±1.3
5	Friability	45.25
6	Swelling (%)	65.23

***In vitro* dissolution studies**

Fig. 33 shows the release pattern of KTE for batch OB in *in vitro* dissolution studies.The Drug release of OB was 68.32 %.

Conclusion:

ketoprofen, an NSAID, was selected as a model for preparation of fast dissolving tablets by Wet granulation technique. Fast dissolving tablets were prepare by adding different concentrations of super disintegrants and several formulae of ketoprofen FDTs have been prepared, utilizing different excipients. Masking taste of bitterness characters of Ketoprofen has been done to decrease compliance for formulated tablets. All prepared FDTs were evaluated for weight variation, thickness uniformity, friability, hardness, wetting time, water absorption time, dispersion time, disintegration time, and dissolution time. All the ketoprofen FDT formulations satisfied the requirements of FDA. Finally, it can be concluded that, the ‘‘patient-friendly dosage form’’ of bitter drugs, especially for pediatric, geriatric, bedridden and non-cooperative patients, can be successfully formulated using this novel wet granulation technique.

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