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Formulation, Evaluation and Pharmacokinetics of Flurbiprofen Fast Dissolving Tablets

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Authors' contributions

This work was carried out in collaboration between all authors. Author PRV designed the method, wrote the first draft of manuscript. Author SRM has reviewed the various literatures, formulated and evaluated all the parameters and also wrote the complete manuscript. All authors read and approved the final manuscript.

Research Article

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ABSTRACT

Aim: The intent of present study is to formulate fast dissolving tablets of flurbiprofen using different superdisintegrants to improve the dissolution and bioavailability.
Place and Duration of Study: Jyothishmathi Institute of Pharmaceutical Sciences, Karimnagar, Andhra Pradesh, India, between January 2011 and December 2012.
Methodology: Flurbiprofen fast dissolving tablets were prepared using different superdisintegrants and characterized for different physical parameters, DSC, FTIR studies, *in vitro* dissolution studies and *in vivo* pharmacokinetics to prove the enhancement of bioavailability.
Results: From the *in vitro* dissolution studies, the percent drug release in 15 min (Q15) was found to be 91.46±1.42% in case of optimized formulation where as the conventional tablets prepared by similar manner showed 22.92±0.47% in 15 min. The initial dissolution rate and dissolution efficiency for optimized formulation was 6.10%/min and 53.44 but it was 1.53%/min and 10.96 in conventional tablets. They increased by 4.0 folds when compared to conventional tablets. From the pharmacokinetic evaluation, the optimized fast dissolving tablets produced peak plasma concentration (C_{max}) as 11433.32 ng/ml at 2 h T_{max}, but they were found to be 8792.64 ng/ml at 3 h $T_{max,}$ in case of conventional tablets. The area under the curve for the optimized fast dissolving and conventional

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tablets were found to be 42691.23 and 30727.14 ng-h/ml.
Conclusion: In summary, formulation of fast dissolving tablets using superdisintegrants was a good approach to enhance the dissolution and absorption rates of flurbiprofen.

Keywords: Bioavailability; conventional tablets; dissolution efficiency; initial dissolution rate; pharmacokinetics; superdisintegrants.

1. INTRODUCTION

Poorly water soluble drugs (Class II drugs) are related to slower rate of absorption from oral route and dissolution rate is the rate limiting step [1]. Thus there is a need to improve the dissolution rate of these drugs to maximize the therapeutic activity [2]. The enhancement of dissolution rate can be achieved by various conventional methods like direct compression, wet granulation, molding, spray drying, freeze drying, and sublimation [3-4]. In these, wet granulation and direct compression methods are simple and easy to manufacture tablets. Conventional equipment and commonly available excipients are involved in these methods [5-6]. The basic approach in development of fast dissolving tablets (FDT) is use of superdisintegrants that plays a vital role in the disintegration and dissolution of tablet. The selection of a suitable disintegrant and its optimum concentration are able to ensure fast disintegration and rapid dissolution rates. Superdisintegrants provide fast disintegration due to collective effect of swelling and water absorption by the tablet. Due to swelling of super disintegrating agent, the wetted surface of the carrier increases that promote the wettability and dispensability of the system, leads to enhance the disintegration and dissolution [7-9].

The objective of the present study is to enhance the dissolution rate of Flurbiprofen (FLB) tablets using superdisintegrants. The presence of superdisintegrant lowers the disintegration time without much affecting the tablet properties. FLB is a phenylalkanoic acid derivative and classified as non-steroidal anti-inflammatory drugs, which are widely used for the long-term treatment of chronic rheumatic diseases [10]. FLB is classified as poorly water soluble class II drug and it is primarily intended to treat painful conditions, which requires fast release of drug [11]. Thus an attempt is made to develop the FLB fast dissolving tablets to give fast dissolution rate to achieve rapid onset of action.

2. MATERIALS AND METHODS

2.1 Materials

Flurbiprofen was a gift sample from FDC Limited, Mumbai, India. All the superdisintegrants were gift samples from Matrix laboratories, Hyderabad, India. All other chemicals used were of analytical grade.

2.2 Preparation of Fast Dissolving Tablets

Fast dissolving tablets were prepared by wet granulation method. FLB, superdisintegrants (sodium starch glycolate, L-Hydroxypropyl cellulose, crospovidone, and croscarmellose) and other tabletting excipients were passed through a mesh no 60 and mixed in a poly bag for 5-10 min, and then granules were prepared with the addition of starch paste as binding agent using 18 sieve, dried and sieved to obtain uniform size granules with 22 sieve. The obtained granules were lubricated with aerosil and magnesium stearate for another 5 min blending

using poly bag method and the resultant mixture was directly compressed into tablets with 7 mm round flat punches using 16-station rotary tabletting machine (Cadmach, Ahmedabad, India) at 3500 N compression force. The compositions of the fast dissolving tablets are given in Table 1. The conventional flurbiprofen tablets (control) were prepared in a similar manner without using superdisintegrants.

2.3 Evaluation of Physical Parameters

The prepared tablets were evaluated for physical properties like weight variation, hardness and friability. For determining weight variation, 20 tablets of each formulation were weighed using an electronic weighing balance (AW 120, Shimadzu, Japan). The hardness was calculated using Monsanto hardness tester. Friability was estimated on ten tablets in a Roche friabilator (Electro lab, Mumbai, India).

2.4 Drug Content Determination

For assessment of drug content, ten tablets were powdered, and the aliquot of powder equivalent to 100 mg of drug was dissolved in appropriate quantity of methanol and 1.2 pH buffer solution. Solution was filtered, diluted and drug content determined by UV-Visible spectrophotometer (Systronics, India) at 247nm.

2.5 *In vitro* Disintegration Time

In vitro disintegration time was determined by Gohel method. In this, 10 ml of water at room temperature was taken in a petridish of 10 cm in diameter. The tablet was then placed carefully in the centre of petridish and the time required for the tablet to completely disintegrate into fine particles was noted. For each formulation, measurements were taken in triplicates [12].

2.6 *In vitro* Dispersion Time

In vitro dispersion time was determined by dropping a tablet in a measuring cylinder containing 6 ml of simulated saliva fluid (pH 6.8). Three tablets from each formulation were randomly selected and *in vitro* dispersion time is expressed in sec [13].

2.7 Wetting Time

Wetting time was determined using following procedure. Briefly, two circular tissue papers were placed in a Petri dish of 10 cm diameter. 10 ml of water containing 0.5 % w/v of phenol red was added to the petridish. A tablet was carefully placed at the surface of the paper in the petridish and the time required for water to reach the upper surface of tablet was noted as wetting time. Wetting time was recorded using stop watch and the measurements were carried out in triplicates for each formulation [14].

Table 1. Formulation of FLB FDTs using different superdisintegrates

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	Control
Flurbiprofen	50	50	50	50	50	50	50	50	50	50	50	50	50
Croscarmellose sodium	4	8	16	-	-	-	-	-	-	-	-	-	-
Crospovidone	-	-	-	4	8	16	-	-	-	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	4	8	16	-	-	-	-
L-Hydroxypropyl cellulose	-	-	-	-	-	-	-	-	-	4	8	16	-
Starch	-	-	-	-	-	-	-	-	-	-	-	-	20
Microcrystalline cellulose	98	94	86	98	94	86	98	94	86	98	94	86	82
Mannitol	40	40	40	40	40	40	40	40	40	40	40	40	40
Aspartame	2	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil	4	4	4	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200	200	200	200	200	200	200

2.8 Water Absorption Ratio

The weight of the tablet prior to placement in the petridish was noted (W_b) using digital balance (Shimadzu, Japan). The wetted tablet was removed and reweighed (W_a). Water absorption ratio (R), was then calculated according to the following equation [15].

$$R = \frac{W_a - W_b}{W_b} \times 100$$

W_b and W_a were tablet weights before and after water absorption, respectively.

2.9 *In vitro* Dissolution Study

The i*n vitro* dissolution studies of FLB tablets was carried out using USP XXIV Type II dissolution apparatus (Electro lab, TDT-08L) at a rotation speed of 50 rpm. The drug release studies were carried out using 900 ml of 1.2 pH buffer as dissolution media at 37º C. An aliquot of 5 ml was collected at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered, by passing through 0.45 µm membrane filters (Millipore, USA) and analyzed at 247 nm using double beam UV-Visible spectrophotometer.

2.10 Calculation of Dissolution Parameters

To explain the improvement of dissolution rate, various dissolution parameters were calculated and compared with conventional tablets. Cumulative percent drug release was plotted as a function of time and percent drug release in 15 min (Q_{15}) was calculated. Initial dissolution rate (IDR) was calculated as percentage dissolved of drug over the first 15 min per min. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [16]. Relative dissolution rate (RDR) is the ratio between amount of drug dissolved from optimized formulation and that dissolved from the conventional formulation at 15 min [17].

2.11 Drug-Excipient Interaction Studies

Differential scanning Calorimetry (DSC) study was carried out on pure drug, crospovidone and optimized formulation to determine the possible interactions. Thermograms were obtained using DSC (Perkin-Elmer, Shelton, U.S). The analyses were performed under nitrogen (nitrogen flow rate 50 ml/min) in order to eliminate oxidative and pyrrolytic effects at a standard heating rate of 15ºC/min over a temperature range of 50ºC - 350ºC.

The fourier transform infrared spectra (FTIR) of flurbiprofen and optimized formulation was recorded between 400 to 4000 cm^{-1} on FTIR to detect the drug-excipient interactions. The FTIR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer (Perkin Elmer FTIR, Perkin Elmer Inst. USA).

2.12 Stability Studies

To evaluate the drug and formulation stability, stability studies were done according to ICH guidelines. Optimized formulation was sealed in aluminum packaging coated inside with polyethylene, and three replicates were kept in the humidity chamber maintained at 40±2 ºC and 75±5% RH for six months [18]. Samples were collected after six months of storage and analyzed for the drug content and *in vitro* dissolution rate and they were subjected to statistical analysis using paired *t*-test to test the significance of difference at 0.05 level of significance [19].

2.13 *In vivo* Study Design

In this current study a crossover study was designed using six human volunteers and divided into two equal groups (group I and group II). All the selected volunteers were non-alcoholics, non-smokers, in the age group of 25 to 33 years and body weight ranging from 57 to 68 kg. The required biochemical tests were carried out to ensure the volunteers were free from both liver and kidney dysfunction and no one was on any drug treatment ten days prior to participation in the study. In the first phase, group I volunteers (n=3) received the conventional tablet (dose=50 mg) whereas group II (n=3) volunteers received optimized fast dissolving tablet (dose=50 mg). The volunteers received the tablets on an empty stomach with sufficient quantity of water (200 ml), and then a standard breakfast was served after 2 h of the study. At regular time intervals lunch and dinner were served in standard quantity. In the second phase, after ten days of washout period, group I volunteers received optimized fast dissolving tablet and group II volunteers received conventional tablet. Blood samples (5 ml) were collected at 0, 0.125, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h in vials in both the cases. The institutional ethical committee (Approval No. 2A91-03/JIPS/KNR/IHEC/2012) approved the protocol of the *in vivo* study FLB fast dissolving tablets in human volunteers.

2.14 HPLC Analysis of FLB Plasma Samples

The above gathered blood samples were centrifuged at 3500 rpm for 20 min to separate the serum and transferred to 5 ml tubes. To the 1 ml of above serum 1 ml of acetonitrile was added and centrifuged for 15 min at 3000 rpm and the supernatant liquid was separated and stored at -40ºC until the analysis of sample for unchanged drug. Then the plasma samples were analyzed for FLB in human plasma using HPLC method. The chromatographic procedures were carried out on Water's HPLC equipped with C18 column and UV detector [20]. Mobile phase used for the analysis consists of phosphate buffer pH 3.5: acetonitrile aqueous solution in the ratio of 50:50, filtered through a 0.45 µm membrane filter and pumped through the column Symmetry C18 (X Terra, 4.6 x 150 mm) at a flow rate of 1 ml/min. FLB stock solution (1mg/ml) was prepared using mobile phase and then working standards of 200, 400, 600, 800 and 1000 ng/ml solutions were prepared. Then the column was equilibrated for 30 min with the mobile phase before going to inject the drug samples. The analysis was carried out at ambient temperature and the run time was set to 8 min. The eluents were analyzed at 254 nm using UV detector.

2.15 Pharmacokinetic Analysis

To explain the FLB behavior in plasma, the required pharmacokinetic parameters were calculated using FLB plasma concentration-time data. Pharmacokinetic parameters from plasma data were estimated using *PK* Solver (version 2.0) for each subject. Non-

compartmental analysis was used. From the plot of time versus plasma concentration, the peak plasma concentration (C_{max}) and the time to reach peak plasma levels (T_{max}) were obtained. From linear part in the elimination phase of a semi-log plot of concentration versus time, the elimination rate constant (ke) was calculated. Finally the absorption rate constant (ka) was calculated from the linear part of residual line using residual method to prove the fast absorption. The area under the curve (AUC) was calculated using the trapezoidal rule.

2.16 Statistical Analysis

The determined pharmacokinetic parameters of both conventional and optimized fast dissolving tablets of FLB were subjected to statistical analysis with paired *t*-test to test the significance of difference at 0.05 level of significance (LS). A value of $P<0.05$ was considered statistically significant.

3. RESULTS

3.1 Evaluation of Physical Parameters

The physical properties of FLB fast dissolving tablets were given in Table 2 and 3. In weight variation test, the pharmacopoeial limit for the tablets is not more than 7.5% of the average weight. The average weight deviation of all tablet formulations was found to be 197.68±1.52-206.34±1.00 mg and within the above mentioned limit, hence all tablet formulations passed the uniformity of weight as per requirements of Indian Pharmacopoeia, 1996. The hardness of the tablets was found to be in the range of 2.9±0.32 to 3.7±0.30 kg/cm^2. The percentage friability for all formulations was below 1%, indicating that the friability is within the prescribed limits. The tablets were found to contain 97.48±0.26-99.82±0.81% of the labeled amount indicating uniformity of drug content. The *in vitro* disintegration time of all tablet formulations was found in the range of 61.32 ± 0.14-36.27 ± 0.58 sec. Among all the above formulations F6 showed rapid disintegration (36 sec). *In vitro* dispersion time of the prepared tablets was found in the range of 79.46±0.88-64.62±0.38 sec. The wetting time of formulated tablets was found in the range of 44.28±1.68-30.12±1.14 sec and water absorption ratio was 38.48 ± 1.14-48.22 ± 1.61.

Table 2. Physical evaluation of FLB fast dissolving tablets

Formulation	Weight variation*(mg)	Hardness** (kg/cm^2)	Friability (%)	Drug content uniformity*** (%)
F1	204.56±0.94	2.9±0.32	0.32	98.14±0.63
F2	198.92±1.73	3.5±0.22	0.37	98.54±1.05
F3	206.34±1.00	3.5±0.26	0.32	99.18±0.81
F4	202.46±0.76	2.9±0.32	0.38	97.72±1.35
F5	204.42±0.57	3.7±0.30	0.29	99.03±0.66
F6	199.34±1.52	3.2±0.15	0.42	99.82±0.81
F7	200.76±1.04	3.5±0.26	0.36	97.71±1.35
F8	202.34±1.09	3.3±0.42	0.31	98.63±1.05
F9	197.68±1.52	3.6±0.41	0.32	99.42±0.95
F10	199.48±0.42	3.2±0.24	0.34	98.36±0.43
F11	204.62±0.78	3.1±0.65	0.39	97.48±0.26
F12	201.48±1.24	3.4±0.28	0.42	99.62±0.68

** All results correspond to avg ± SD, n=20; ** All results represent avg ± SD, n=6; *** All results represent avg ± SD, n=3*

Table 3. Physical evaluation of FLB fast dissolving tablets

Formulation	In-vitro disintegration time* (sec)	In-vitro dispersion time* (sec)	Wetting time* (sec)	Water absorption ratio*	Q_{15}*
F1	46.24 ± 0.24	76.31±0.56	34.45±1.32	42.56 ± 1.52	54.82±1.47
F2	42.18 ± 0.32	78.46±0.24	44.28±1.68	40.16± 1.92	62.37±1.87
F3	39.28 ± 0.56	68.45±0.76	30.12±1.14	44.26± 1.74	72.49±0.36
F4	52.72 ± 0.24	79.34±0.84	31.84±1.12	38.48 ± 1.14	56.34±0.32
F5	48.38 ± 0.76	71.26±0.28	38.64±1.18	39.24± 1.46	72.64±0.56
F6	36.27 ± 0.58	64.62±0.38	30.28±1.44	45.16 ± 1.52	91.46±1.42
F7	59.28 ± 0.52	76.48±0.62	42.14±1.15	48.22 ± 1.61	46.88±1.32
F8	49.74 ± 0.44	74.42±0.45	41.38±1.24	41.45 ± 1.43	49.54±0.23
F9	47.42 ± 0.48	67.56±0.46	34.63±1.46	44.28 ± 1.22	53.81±1.46
F10	61.32 ± 0.14	79.46±0.88	42.14±1.15	44.76 ± 1.44	39.29±0.69
F11	50.48 ± 0.42	76.22±0.43	41.38±1.24	41.52 ± 1.68	44.38±0.98
F12	48.63 ± 0.18	69.24±0.86	34.63±1.46	46.56 ± 1.59	46.32±0.92

** All results represent avg ± SD, n=3*

3.2 *In vitro* Dissolution Study

The mean cumulative percent of FLB released from FDTs including different amounts of superdisintegrants (F1-F12) was found to be in the range of 39.29±0.69%-91.46±1.42% in 15 min. Among all the formulations, the optimized formulation F6 showed the 91.46±1.42% drug release in the 15 min where as the conventional FLB tablets prepared by similar manner showed 22.92±0.47% in 15 min (Fig. 1). Thus the formulation F6 was considered better among other formulations to produce fast release of the FLB.

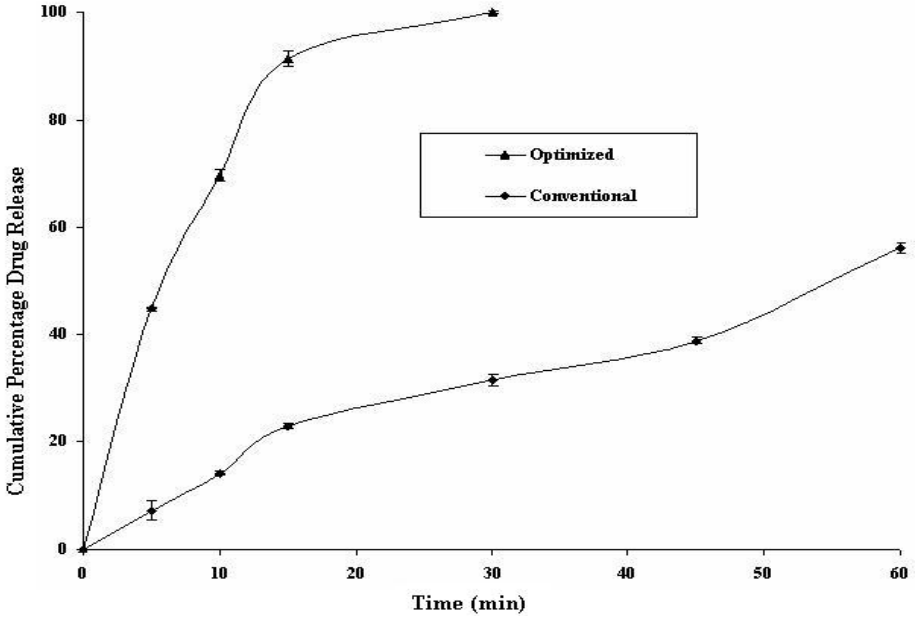

Fig. 1. Comparison of drug release from FLB optimized and conventional tablets

The percent drug release in 15 min (Q_{15}) and initial dissolution rate (IDR) for optimized formulations were 91.46±1.42%, 6.10%/min respectively. These were very much higher compared to control tablet (22.92±0.47%, 1.53%/min). The improvement in the dissolution characteristics of a drug described in terms of dissolution efficiency (DE) and relative dissolution rate (RDR). The RDR was found to be 3.98 for F6. The DE was found to be 53.44 for optimized formulation and it is increased by 4.0 folds with optimized FDT formulation when compared to control tablet (10.96) (Table 4).

Table 4. Dissolution parameters of optimized and conventional FLB formulations

Formulation	(Q_{15})	IDR (%/min)	DE	RDR
Optimized (F19)	91.46±1.42	6.10	53.44	3.98
Conventional	22.92±0.47	1.53	10.96	

Q_{15}-percent drug release in 15 min, IDR-initial dissolution rate, DE-dissolution efficiency and RDR-relative dissolution rate.

3.3 Drug-polymer Interaction Studies

DSC studies were conducted to study the nature of FLB in the formulated tablets. DSC curves obtained for pure drug, crospovidone and optimized formulation were showed in Fig. 2. A sharp endothermic peak equivalent to the melting point of FLB was found at 116ºC. An endothermic peak related to the melting point of FLB in optimized formulation was observed at 115.6ºC. The FTIR analysis of pure FLB and optimized formulation were showed the principal peaks at similar wave numbers (Fig. 3). The FTIR spectral analysis of pure FLB showed the principal peaks at wave numbers of 1701.22, 1415.75, 1217.06, 923.9, 765.7and 696.23 cm^{-1}. In the FTIR spectra of the optimized formulation were 1701.22, 1419.61, 1217.06, 925.83, 765.7and 696.23 cm^{-1} wave numbers were observed.

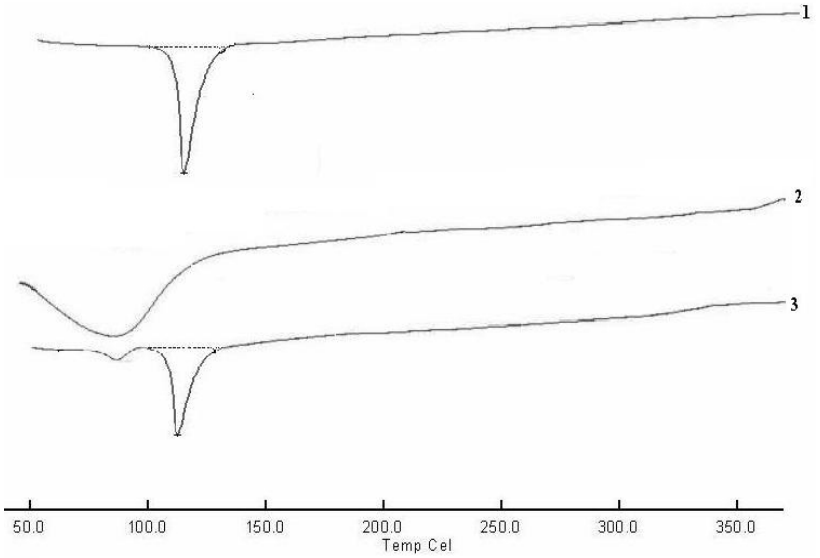

Fig. 2. DSC thermograms of 1) Flurbiprofen 2) Crospovidone 3) Optimized formulation

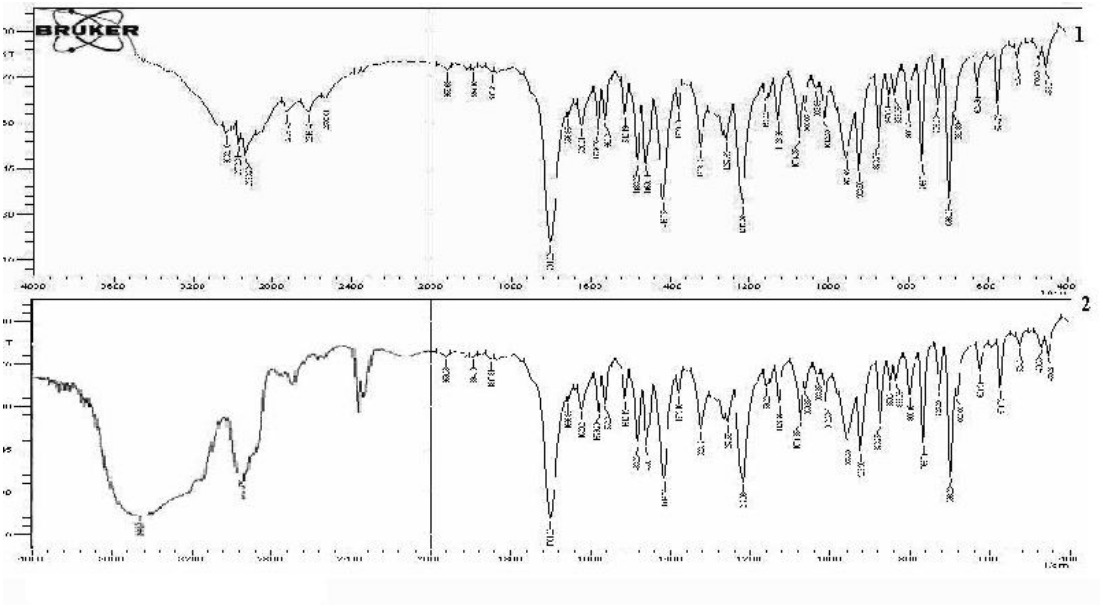

Fig. 3. Fourier transform infrared spectra of 1) Flurbiprofen 2) Optimized formulation

3.4 Stability Studies

To check the stability of tablet formulations, stability studies were carried out for six months. After storage of six months, the formulation was subjected to a drug content and *in vitro* dissolution studies and from the statistical analysis there was no significant difference between before and after storage (P<0.05).

3.5 Pharmacokinetics in Healthy Volunteers

In this experiment, pharmacokinetic evaluation was carried out for both conventional and optimized formulation. The mean FLB plasma concentrations of six human volunteers following the oral administration of both tablets were showed in Fig. 4 and the mean pharmacokinetic parameters from the *in vivo* experiments of both tablets were given in Table 5.

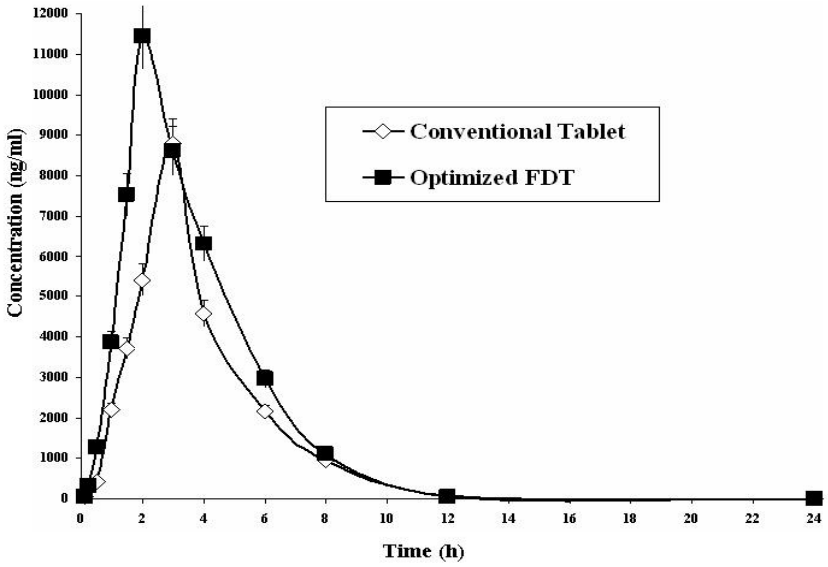

Fig. 4. Time versus mean plasma concentration profiles of FLB following the oral administration of optimized and conventional tablets in human volunteers

Table 5. Pharmacokinetic parameters of FLB optimized FDT and conventional tablet (Avg±SD n=6)

Parameters	Conventional tablet	Optimized FDT	*t*-test at 0.05 LS
ka (1/h)	0.41±0.01	0.49±0.01	Not Significant
ke (1/h)	0.34±0.01	0.37±0.01	Not Significant
Tmax (h)	3.00±0.01	2.00±0.01	Significant
Cmax (ng/ml)	8792.64±472.48	11433.32±184.28	Significant
AUC 0-inf (ng/ml*h)	30727.14±410.32	42691.23±464.68	Significant

4. DISCUSSION

The aim of present research is to improve the dissolution and absorption rates of a water insoluble FLB with the help of superdisintegrants. In this study, FLB fast dissolving tablets were prepared using different superdisintegrants in different ratios and evaluated for different physical parameters, DSC, FTIR studies, *in vitro* dissolution studies and *in vivo* pharmacokinetics to prove the rapid dissolution rate and enhanced bioavailability.

Weight variation, thickness, hardness and friability of all the tablet formulations were complied with pharmacopoeial standards, so all the tablets were with acceptable physical characteristics. In weight variation test, the pharmacopoeial limit for tablets is not more than 7.5% of the average weight. The average percentage deviation of all tablet formulations was found to be within the specified limit and hence all the formulations passed the uniformity of weight as per the requirements of Indian Pharmacopoeia. From the physical characterization, all the tablet formulations were uniform in hardness, friability and drug content uniformity. Among all the formulations, formulation F6 showed rapid disintegration (36 sec) and also showed rapid in vitro dispersion time. This is due to superior action of

crospovidone as a super disintegrant. Similar type of results was observed in the study developed by Vemula et al. In both the studies, superdisintegrants were used to enhance the dissolution of FLB, but in the present study, 8% crospovidone with wet granulation method showed fast disintegration where as in the study by Vemula et al. [21], used 10% crospovidone by direct compression method. The wetting time is closely related to the inner structure of the tablet and is mimics the action of saliva in contact with the tablet to illustrate the water uptake and subsequent wetting of tablet. In contrast to conventional tablets, the rapid wetting time was observed in almost all formulations may be due to ability of swelling and also capacity of water absorption by superdisintegrants.

From the results of *in vitro* drug release studies, the dissolution rate of FLB was enhanced significantly as increasing the superdisintegrant concentration level from 2 to 8% w/w. In comparison of the two methods, wet granulation method showed superior in dissolution rate than direct compression method. All the formulations showed rapid disintegration and fast dissolution rate when compared with conventional tablets. Among all the formulations, formulation with 8% crospovidone showed fast dissolution rate and it was increased nearly 4 times when compared to conventional tablets. This can be well correlated with the disintegration time and wetting time which were very lower for the formulation with 8% crospovidone than the other formulations. Similar type of results was observed with fast dissolving tablets in the study developed by Neduri et al. This improvement is due to the presence of superdisintegrant and they provide quick disintegration due to combined effect of swelling and water absorption by tablets [8]. Due to swelling of superdisintegrant, the wetted surface of the carrier increases that promote the wettability and dispersibility of the system, leads to improve the disintegration and dissolution rate [7].

Overall increase in the dissolution performance of the optimized formulations described in terms of dissolution parameters (IDR, DE, RDR) compared to control tablet could be due to the lesser disintegration time and increased wettability and dispersibility of tablets. The optimized formulation showed 4 times improvement in dissolution parameters in comparison with conventional tablets. Similar type of improvement in IDR, DE, RDR was reported in the study of Vemula et al. [10] i.e., formulation of flurbiprofen tablets. In summary, the development of fast dissolving tablets may be the simple and promising option to achieve the fast dissolution rate of poorly soluble drugs like FLB. Further the pharmacokinetic evaluation is needed to prove the capability of fast dissolving tablets to improve the bioavailability of FLB and the optimized formulation was selected for further pharmacokinetic studies.

DSC studies were performed to understand the nature of the drug in the formulated tablets. Thermogram of the optimized formulation did not show any significant shift in the endothermic peak when compared to pure drug, indicating that there was no physical change in drug. From the FTIR spectral analysis all the principal peaks observed in pure drug were present in the FTIR spectra of the optimized formulation and some additional peaks were observed with physical mixtures, which could be due to the presence of polymers. These results suggest that there is no interaction between the drug and polymers used in the present study. After storage of six months, the formulation was subjected to a drug assay and *in vitro* dissolution studies and the data showed that there was no significant change in formulation in the sense of drug content and dissolution behavior.

The *in vitro* drug release studies of fast dissolving tablets of FLB revealed that they provide significant improvement in the disintegration time as well as dissolution time. Further the pharmacokinetic evaluation of these tablets in healthy volunteers is needed to prove above

results. From the evaluation, K_a indicates absorption rate and K_e indicates the elimination rate. The T_{max} represents rate of absorption and AUC is related to extent of absorption while C_{max} is related to both. The extent of absorption is an important factor of a formulation hence the AUC is a key parameter for comparative bioavailability study analysis and the others like T_{max} and C_{max} are also important features that related to the therapeutic efficiency of drugs [22].

From the pharmacokinetic evaluation, after oral administration of optimized fast disintegrating tablet and conventional tablet of FLB, the mean plasma concentration-time curve was plotted and showed in Figure 4. From these results of pharmacokinetic parameters, rising in the K_a and K_e values was examined in optimized formulation in contrast to conventional tablet, which indicates the improvement of absorption rate. The optimized fast dissolving tablets produced peak plasma concentration C_{max} was 11433.32 ng/ml at 2 h T_{max}, but they were found to be 8792.64 ng/ml at 3 h $T_{max,}$ in case of conventional tablets. This indicates the significant increase in bioavailability. Similar type of results was reported in Liu et al. [23] i.e., development of lyophilized gliclazide poloxamer solid dispersions [23].

From the estimation of mean area under the curve, the AUC for the optimized fast dissolving and conventional tablets were 42691.23 and 30727.14 ng-h/ml respectively. From these results there was a significant enhancement of AUC of optimized formulation when compared with conventional tablet, which proves the improvement of extent of absorption of FLB. In the reported study by Muraoka et al. [24], similar type of results was observed. By this comparison of pharmacokinetic parameters, it was confirmed that the optimized fast dissolving formulation showed significant enhancement in rate and extent of absorption of FLB in contrast to conventional tablets. From the statistical analysis of pharmacokinetic parameters by paired *t*- test, there was a significant difference in the $C_{max,}$ T_{max} and AUC but there was no significant difference in K_a and $K_{e.}$ In summary, the pharmacokinetic study results showed that the fast dissolving tablets using superdisintegrants is able to improve the absorption rate of FLB than conventional tablets.

5. CONCLUSION

An attempt was made to develop the Flurbiprofen fast dissolving tablets to improve the dissolution rate and absorption rate. Among all the formulations, formulation F6 showed rapid disintegration and rapid *in vitro* dispersion times. Based on *in vitro* drug release studies, F6 formulation showed significant level of drug release at the fast rate almost complete drug release within 15 min. The dissolution efficiency was found to be 53.44 for optimized formulation and it is increased by 4.0 fold with optimized formulation compared with conventional tablet. DSC and FTIR spectral studies showed that there is no interaction between the drug and excipients. The results of the pharmacokinetics in human volunteers showed that the there was a significant improvement of bioavailability in case of optimized fast dissolving tablets when compared to conventional tablets. Thus the formulation of fast dissolving tablets using superdisintegrants was a good approach to enhance the dissolution rate and absorption rate of flurbiprofen.

CONSCENT

All the authors declare that 'written informed consent was obtained from the patient for publication of this work.

ETHICAL APPROVAL

The institutional ethical committee (Approval No. 2A91-03/JIPS/KNR/IHEC/2012) approved the protocol of the *in vivo* study FLB fast dissolving tablets in human volunteers.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Charman WN. Lipids, lipophilic drugs, and oral drug delivery-some emerging concepts. J Pharm Sci. 2000;89(8):967-78.
2. Meyer MC. Bioavailability and bioequivalence of drugs. In: Swarbik J, ed. Encyclopedia of pharmaceutical technology. New York, Marcel Dekker. 1998;33-58.
3. Hirani JJ, Rathod DA, Vadalia KR. Orally disintegrating tablets: a review. Trop J Pharm Res. 2009;8(2):161-72.
4. Bandari S, Mittapalli RK, Gannu R, Rao YM. Orodispersible tablets: An overview. Asian J Pharm. 2008;1:2-10.
5. Dobetti L. Fast-melting tablets: developments and technologies. Pharm Tech. 2000;12(9):32-42.
6. Kaushik D, Dureja H, Saini TR. Mouth dissolving tablets: a review. Ind Drugs. 2004;41:187-93.
7. Vemula SK, Bontha VK, Garrepally P, Chilukala S, Madavapeddi AK. Development and characterization of fast disintegrating tablets of terbinafine hydrochloride. J Pharm Res. 2011;4(7):2273-75.
8. Neduri K, Bontha VK, Vemula SK. Different techniques to enhance the dissolution rate of lovastatin: formulation and evaluation. Asian J Pharm Clin Res. 2013;6(1):56-60.
9. Battu SK, Repka MA, Majumdar S, Rao YM. Formulation and evaluation of rapidly disintegrating feniverine tablets, effect of superdisintegrants. Drug Dev Ind Pharm. 2007;33:1225-32.
10. Vemula SK, Veerareddy PR. Fast disintegrating tablets of flurbiprofen: Formulation and characterization. Lat Am J Pharm. 2011;30(6):1135-41.
11. Wang X, Yu J, Tang X. In vitro release and pharmacokinetics of flurbiprofen sustained-release capsules containing coated pellets. Asian J Pharm Sci. 2007;2(2):77-84.
12. Gohel M, Patel M, Amin A, Agrawal R, Dave R, Bariya N. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. AAPS Pharm Sci Tech. 2004;5(3):1-6.

13. Narmada, GY, Mohini K, Prakash B, Gowrinath DXP, Kumar KS. Formulation, evaluation and optimization of fast dissolving tablets containing amlodipine besylate by sublimation method. Ars Pharm. 2009;50(3):129-44.
14. Bi Y, Sunanda H, Yonezawa Y, Danjo K, Otuska A, Iida K. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem Pharm Bull. 1996;44(11):2121-27.
15. Madan J, Sharma AK, Singh R. Fast dissolving tablets of Aloe vera gel. Trop J Pharm Res. 2009;8(1):63-70.
16. Sammour OA, Hammad MA, Megrab NA, Zidan AS. Formulation and optimization of mouth dissolve tablets containing Rofecoxib solid dispersion. AAPS Pharm Sci Tech. 2006;7(2):E1-E9.
17. Valleri M, Mura P, Maestrelli F, Cirri M, Ballerini R. Development and evaluation of glyburide fast dissolving tablets using solid dispersion technique. Drug Dev Ind Pharm. 2004;30(5):525-34.
18. Chaudhary A, Tiwari N, Jain V, Singh R. Microporous bilayer osmotic tablet for colon-specific delivery. Eur J Pharm Biopharm. 2011;78:134-40.
19. Mathews BR. Regulatory aspects of stability testing in Europe. Drug Dev Ind Pharm. 1999;25:831-56.
20. Veerareddy PR, Vemula SK. Formulation, evaluation and pharmacokinetics of colon targeted pulsatile system of flurbiprofen. J Drug Targ. 2012;20(8):703-14.
21. Vemula SK, Bontha VK, Garrepally P. Development and characterization of fast disintegrating tablets of piroxicam. Inventi Impact: Pharm Tech. 2010;1(3):169-73.
22. Grahnen A. Design of bioavailability studies. Pharm Int. 1984;5:100-03.
23. Liu Y, Liu G, Liu Y, Li S, Jia J, Zhang M, Lu C, Zhang Y, Li X, Yu C. Pharmacokinetic and bioequivalence comparison between orally disintegrating and conventional tablet formulations of flurbiprofen: a single-dose, randomized-sequence, open-label, two-period crossover study in healthy chinese male volunteers. Clin Therp. 2009;31(8):1787-95.
24. Muraoka A, Tokumura T, Machida Y. Evaluation of the bioavailability of flurbiprofen and its betacyclodextrin inclusion complex in four different doses upon oral administration to rats. Eur J Pharm Biopharm. 2004;58:667-71.

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