Journal of Bioequivalence & Bioavailability
ISSN: 0975-0851
Mohd and Vemula, J Bioequiv Availab 2016, 8:2
DOI: 10.4172/jbb.1000274
Research Article Open Access

Formulation and Pharmacokinetics of Vitamin E TPGS Melt Dispersion Granules: An Approach to Improve Oral Delivery of Flurbiprofen

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Abstract

Formulation of solid dispersions using BCS class II drugs is one of the fruitful technologies to improve the drug solubility and dissolution rate to improve the bioavailability, but suffers from poor flowability and stability. To overcome the above problems, present research was intended to prepare the solid dispersions using combination of melt dispersion and surface adsorption methods. In the present study flurbiprofen melt dispersion granules were prepared by incorporating vitamin E TPGS as the carrier material and lactose as an adsorbent to improve the dissolution rate and flowability. Melt dispersion granules were evaluated for angle of repose, solubility studies, differential scanning calorimetry, *in vitro* dissolution studies, stability studies and finally subjected to pharmacokinetic studies. From the differential scanning calorimetry studies, change in the drug peak in formulation revealed the change in drug crystallinity. F4 formulation showed not only good flowability but also complete drug release in 15 min when compared to other formulations and pure drug. From the pharmacokinetic evaluation, F4 formulation showed 1.38-fold higher bioavailability and 1.32-fold higher C_{max} compared to plain flurbiprofen. Hence, the formulated vitamin E TPGS melt dispersion granules were able to improve the dissolution rate as well as the bioavailability of flurbiprofen.

Keywords: Bioavailability; Dissolution rate; Melt dispersion; Solid dispersions; Surface adsorption

Introduction

Oral drug delivery is considered as the most preferable route for chronic treatment of various diseases, due to its greater stability, flexibility in formulation, dosage accuracy, low cost of manufacturing and packaging and patient friendly administration [1]. But most of the drugs belong to poorly water soluble (BCS Class II) category and suffering from poor dissolution and it is worst if given in the form of solid dosage forms like tablets [2]. Hence BCS Class II drugs required to improve the solubility/dissolution to give as oral solid dosage forms. One of the widely used approaches to enhance the solubility and dissolution rate of poorly water soluble drugs is a well-known process of fabricating solid dispersions [3].

Solid dispersions can be defined as the molecular dispersions of drugs in a polymer in solid form and can be prepared by solvent evaporation method and fusion method [4]. In solvent evaporation method, a solvent is employed to dissolve the drug and carrier, and in fusion method, carrier is melted and the drug is dissolved in the melt to obtain the solid dispersions. Once the solid dispersions are obtained they are pulverized to get the desired particle sizes but most of the solid dispersions are suffered from poor flowability and stability that depend on the nature of carrier used. Surface adsorption method is used to absorb the sticky solid dispersion mass on surface of inert carrier to improve the flowability and compressibility. Lactose is one of the widely used inert carrier/diluent, selected as the surface adsorbent due to its inert nature, low cost, good adsorption and compressibility [5]. Hence in the present study combination of melt dispersion and surface adsorption technologies were used to keep the advantages of solid dispersions and to avoid the above disadvantages.

Flurbiprofen (FLB), a poorly water soluble non-steroidal anti-inflammatory drug [6] is selected as the model drug in the present study to study the effect of melt dispersion granules on the dissolution rate when compared to plain drug. Some of the recent research examples on dissolution enhancement of FLB are flurbiprofen gelucire solid dispersions [2]; flurbiprofen sublimated fast dissolving tablets [7], flurbiprofen fast disintegrating tablets [8], flurbiprofen fast dissolving tablets [9] and flurbiprofen solid dispersions [10]. In the present study, FLB melt dispersion granules were prepared using vitamin E TPGS as the hydrophilic carrier to enhance the dissolution rate and lactose as an adsorbent to improve the flowability of formulation. Presence of an active ingredient in solid dispersions can decrease in crystal lattice energy and an increase in surface area that provides the improvement in dissolution. The use of surface adsorbents like lactose can convert the molten sticky mass to free flowing and stable granules. Thus the present study is planned to formulate FLB melt dispersion granules to keep the advantages of both solid dispersions and surface adsorption methods as mentioned above.

Materials and Method

Materials

Flurbiprofen was gift sample from FDC Limited, Mumbai, India. Vitamin E TPGS was obtained as gift samples from Dr. Reddy's Labs, Hyderabad, India. All other reagents used were of analytical grade and obtained from S.D. Fine Chemicals, Mumbai, India.

Preparation of FLB melts dispersion granules

FLB solid dispersions using vitamin E TPGS as carrier were

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Received January 01, 2016; **Accepted** January 22, 2016; **Published** January 29, 2016

Citation: Mohd AB, Vemula SK (2016) Formulation and Pharmacokinetics of Vitamin E TPGS Melt Dispersion Granules: An Approach to Improve Oral Delivery of Flurbiprofen. J Bioequiv Availab 8: 089-94. doi:10.4172/jbb.1000274

prepared by the fusion method. Accurately weighed amounts of FLB and vitamin E TPGS in various ratios were used to prepare the melt dispersions. The carrier material was melted in a petridish using water bath and the drug was dispersed uniformly in the molten carrier. Then the uniform drug-carrier molten mass was cooled to room temperature. During the cooling process, lactose (adsorbent) was added to molten mass and properly mixed to get the homogenous mixture and passed through the sieve # 22 to convert into granules. The resulted melt dispersion granules were packed in amber colour bottles and stored in desiccators until use. All the formulations and their compositions were showed in Table 1.

Solubility studies

From the each prepared formulation an excess amount of FLB melt dispersion granules were transferred into conical flasks which contain 10 ml of media and sonicated for 2 h at room temperature. Then they were placed on a shaker, agitated at room temperature for 48 h and the suspensions were filtered through Whatman filter paper. The filtrate was suitably diluted and analyzed at 247 nm wavelengths using double beam UV-Visible spectrophotometer. The same procedure was repeated with different media for all formulations and plain drug.

Determination of drug content

To estimate the drug content, accurately weighed quantity of prepared melt dispersion granules were transferred to a volumetric flask containing 10 ml of methanol and sonicated for 5 min using bath sonicator. The resulted solution was diluted with suitable media (7.2 pH phosphate buffer), filtered and analyzed for FLB content at 247 nm using double beam UV-Visible spectrophotometer.

Flow properties-Measurement of angle of repose

Angle of repose (θ) is used to determine the frictional force between the granules was measured using fixed funnel method and calculated using the following formula:

$$Tan\ \theta = h/r \quad (1)$$

In which, θ is the angle of repose, h is the height of the cone and r is radius of the cone base. To measure the angle of repose, a funnel was fixed to a stand so that the lower tip of funnel was 2.5 cm above the surface. A graph paper was placed on a flat surface. The powder blend was allowed to fall freely on the graph paper through the funnel (6.8 cm diameter), till the tip (8 mm diameter) of heap formed just touches the funnel. The radius of heap was noted and from this angle of repose was determined.

Differential scanning calorimetry

The thermograms were recorded for plain drug (FLB), vitamin E TPGS, and F4 formulation using differential scanning calorimeter (Shimadzu, Japan). Accurately weighed amount of 5 mg sample was placed in an open aluminium standard pan was heated at a scanning rate of 50 C/min from a temperature 0 to 450°C under a nitrogen gas flow.

Formulation Code	FLB: Vitamin E TPGS Ratio (w/w)	Solid dispersion: Lactose Ratio (w/w)
F1	1:0.1	1:1
F2	1:0.2	1:1
F3	1:0.3	1:1
F4	1:0.4	1:1
F5	1:0.5	1:1.5
F6	1:0.6	1:2

Table 1: Formulation of FLB melt dispersion granules using vitamin E TPGS.

In vitro dissolution study

USP XXVI Type II dissolution apparatus (Electro lab, TDT-08L) was used to conduct the in vitro dissolution studies at a rotation speed of 50 rpm, and temperature of 37 ± 0.5°C. The dissolution studies of plain drug, marketed tablet and melt dispersion granules equivalent to 50 mg of FLB were carried out in 900 ml of 7.2 pH phosphate buffer. At standard time intervals 5 ml of sample was collected and replaced with fresh dissolution medium. The samples were filtered through 0.45 µm membrane filter (Millipore, USA) and analyzed spectrophotometrically at 247 nm.

Calculation of dissolution parameters

Dissolution data from above study was further analyzed and compared with plain drug and marketed tablets for percent drug release in 15 min (Q_{15}), initial dissolution rate (IDR), relative dissolution rate (RDR) [11], dissolution efficiency (DE) and mean dissolution time (MDT) [12].

Stability studies

The stability of F4 meld dispersion granules was monitored up to 3 months at ambient temperature (30°C) and relative humidity (65% RH) in stability chamber. Samples were removed periodically and evaluated for drug release. The similarity factor (f_2) was calculated between dissolution rates of tablets before and after storage [13]. The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) of dissolution between the two curves.

$$f_2 = 50 \text{ x } \log\left\{\left[1 + (1/n)\ \Sigma_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \text{ x } 100\right\} \quad (2)$$

In vivo bioavailability studies

Bioavailability studies of FLB melt dispersion granules were approved by the institutional animal ethical committee (Approval No. FMDG/2013/6). In this study, bioavailability of FLB melt dispersion granules (F4 formulation) was compared with FLB plain drug dispersed in sodium carboxy methyl cellulose. Twelve male Wistar rats weighing 200-220 g were used in this study and were fasted overnight but had free access to water. In the present study twelve rats were divided into two equal groups. Group I animals received plain drug (dose 50 mg) whereas group II rats received melt dispersion granules (dose 50 mg). Blood samples (0.5 ml) were collected by retro-orbital venous plexus puncture with the aid of glass capillary at 0.125, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h post oral dose. All samples were collected in EDTA coated Eppendorf tubes. Plasma was separated by centrifuging at 3000 rpm for 10 min and the supernatant plasma was separated and stored at -40°C until the analysis of sample for unchanged drug.

HPLC analysis of FLB in plasma

FLB concentration in plasma samples was determined using HPLC method adopted from Vemula et al. [14]. The plasma sample was injecting into the HPLC column (loop volume 20 µl and flow rate 1 ml/min) and the analysis was performed at ambient temperature (8 min run time). The eluents were monitored at 254 nm using UV detector.

Pharmacokinetic analysis

Pharmacokinetic parameters were estimated using PK Solver (version 2.0) for each subject by non-compartmental analysis. The peak plasma concentration (C_{max}) and the time to reach peak plasma levels (T_{max}) were directly obtained from the plot of time versus plasma concentration. The area under the curve (AUC) was calculated using

the trapezoidal rule. The area under first moment curve (AUMC) was obtained from the plot of product of plasma drug concentration and time versus time. The mean residence time (MRT) is calculated from the ratio of AUMC to AUC. The relative bioavailability of FLB melt dispersion granules was calculated against FLB suspension using AUC of both.

Statistical analysis

The calculated pharmacokinetic parameters were subjected to statistical analysis using analysis of variance (ANOVA) to test the significance of difference. A value of $P<0.05$ was considered statistically significant.

Results

Solubility studies of FLB solid dispersions

Solubility studies of plain FLB and its melt dispersion granules were conducted in different media and the results were shown in Table 2. FLB solubility was highly pH-dependent hence determined in different media, i.e., 0.1 N HCl, distilled water and phosphate buffer pH 7.2. It was observed that as the increase in pH of the media increased the solubility i.e. FLB showed greatest solubility in 7.2 pH phosphate buffer. As the carrier concentration increases, the solubility increased proportionally up to 1:0.4 ratio and after that no significant increase in solubility by increasing the carrier ratio.

Determination of drug content

Determination of drug content was mainly to check the significant loss of drug during the formulation of solid dispersions/melt dispersion granules. In the present study, all the formulations showed 95-101% w/w of FLB that indicated the method does not had any significant loss of drug during drug incorporation into carrier.

Differential scanning calorimetry

DSC thermograms of plain FLB and F4 formulation were showed in Figure 1. DSC studies give information about melting, crystallization, decomposition or change in a heat capacity that explains the physicochemical status of the drug and its interaction with carrier. A sharp endothermic peak corresponding to the melting point of FLB was found at 116°C in plain drug but in case of F4 formulation FLB showed broad peak at 125°C. This indicates the change in crystalline state of FLB.

Flow properties-measurement of angle of repose

The results of angle of repose less than 40° indicates fair to passable flow properties of the powder mixture. Plain FLB showed greater than 40° angle of repose indicated the poor flow. All the solid dispersions using vitamin E TPGS were formed sticky mass which was difficult to pass through sieve. To overcome this problem lactose was used as surface adsorbent and all formulations showed good flowability and the values were given in Table 3. As the concentration of carrier increases more than 1:0.4 ratio, it requires more than 1 g lactose to give good flow.

Formulation Code	FLB solubility in mg/ml		
	0.1 N HCl	Distilled Water	7.2 pH Buffer
Pure FLB	0.069 ± 0.15	0.167 ± 0.11	0.204 ± 0.16
F1	0.124 ± 0.16	0.298 ± 0.12	0.435 ± 0.29
F2	0.141 ± 0.12	0.378 ± 0.25	0.541 ± 0.18
F3	0.159 ± 0.18	0.476 ± 0.22	0.582 ± 0.11
F4	0.172 ± 0.32	0.567 ± 0.18	0.648 ± 0.27
F5	0.176 ± 0.21	0.569 ± 0.11	0.651 ± 0.14
F6	0.178 ± 0.12	0.572 ± 0.28	0.654 ± 0.21

Table 2: Solubility of FLB-vitamin E TPGS melt dispersion granules in various solvents (mg/ml).

In vitro dissolution study

Figure 2 was shown the drug release pattern of F1-F6 formulations and Figure 3 represents comparison between F4 melt dispersion granules and plain drug and marketed tablet. From the in vitro dissolution studies, F4 formulation showed fast dissolution (99.02 ± 1.07% in 15 min) than other formulations and improved significantly when compared to plain drug and marketed tablet.

Calculation of dissolution parameters

All the calculated dissolution parameters were given in Table 3. Q15 and IDR values of F4 formulation was found to be 99.28 ± 0.96%, 6.619%/min and significant improvement was observed when compared to plain drug and marketed tablets. The DE of F4 melt dispersion granules was found to be 76.73 and it is increased by 10-fold when compared to plain drug and 3.5-fold compared to marketed tablets. MDT values were given in Table 3 and shown low value in case of melt dispersion granules.

Stability studies

The stability of F4 melt dispersion granules was carried and the

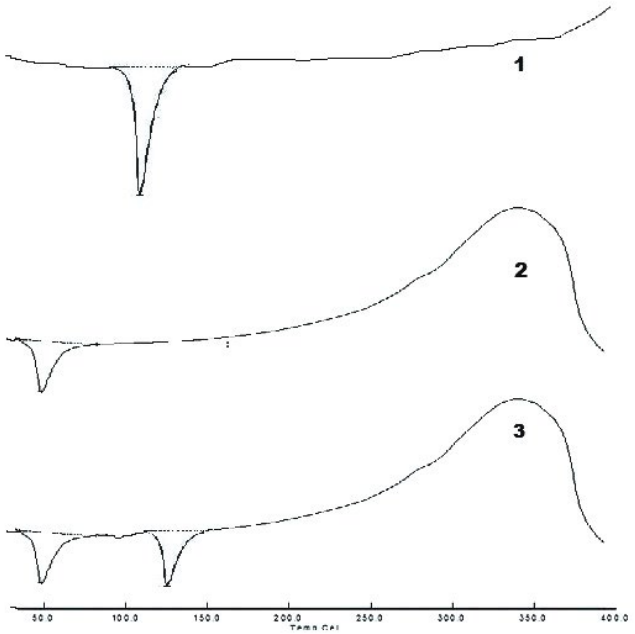

Figure 1: DSC thermograms of 1) FLB 2) Vitamin E TPGS 3) F4 melt dispersion granules.

Formulation	Q_{15} (%)	DE_{30} (%)	IDR (%/min)	MDT (min)	Angle of Repose (°)
Plain drug	7.12 ± 1.32	7.33	0.475	14.60	47.28 ± 1.42
Marketed tablets	23.64 ± 1.87	21.54	1.576	14.46	-
F4 Melt dispersion granules	99.28 ± 0.96	76.73	6.619	7.28	28.43 ± 1.27

Table 3: Determination of dissolution parameters and angle of repose (Mean ± SD, n=3).

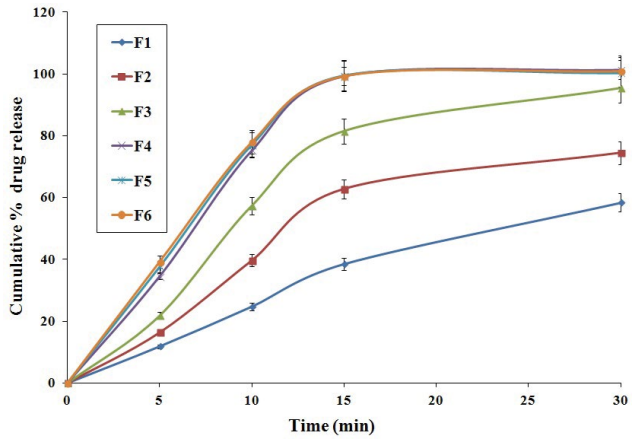

Figure 2: *In vitro* dissolution studies of F1-F6 melt dispersion granules (n=3).

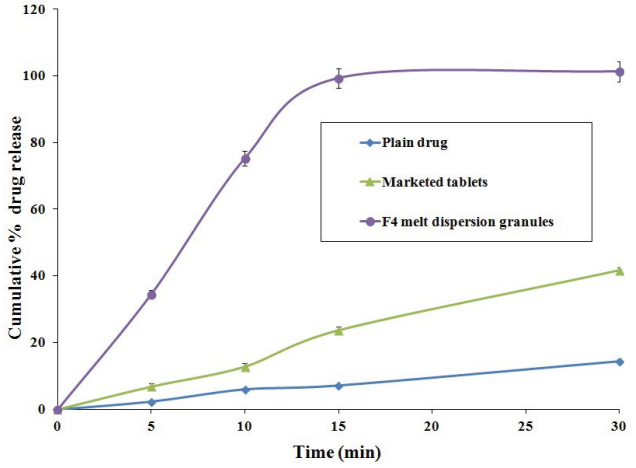

Figure 3: Comparison of FLB release from plain drug, marketed tablets and F4 melt dispersion granules (n=3).

Time (min)	Before storage	After 3 months storage	*t*-test at 0.05 LS	Similarity Factor (f_2)
0	0.00 ± 0.00	0.00 ± 0.00	Not Significant	84.58
5	34.56 ± 1.12	32.12 ± 1.23		
10	75.28 ± 1.34	73.89 ± 0.98		
15	99.28 ± 0.96	97.12 ± 1.07		

Table 4: Stability studies of FLB F4 melt dispersion granules (n=3).

samples were tested for dissolution after 3 months of storage. From the statistical analysis there was no significant difference between before and after storage (P<0.05) and the similarity factor (f2) was found as 84.58 between before and after storage of 3 months Table 4.

Pharmacokinetic analysis

In this experiment, pharmacokinetic evaluation was carried out for both F4 melt dispersion granules and plain drug suspension. The mean FLB plasma concentrations following the oral administration of both were showed in Figure 4 and the mean pharmacokinetic parameters of both were given in Table 5. In the above pharmacokinetic parameters, T_{max} represents rate of absorption and AUC is related to extent of absorption while C_{max} is related to both.

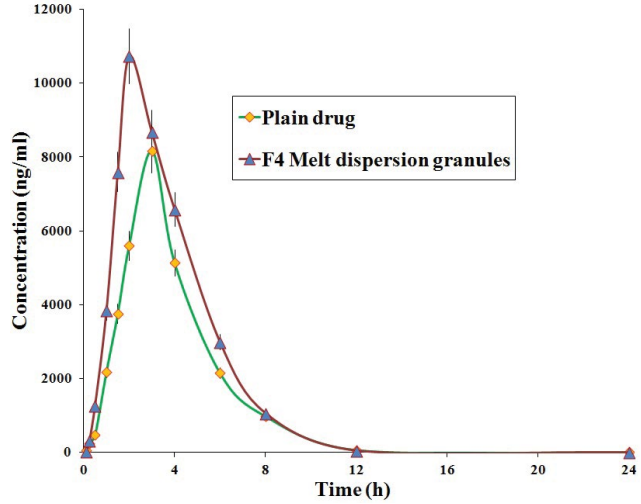

Figure 4: *In vivo* plasma concentrations of FLB plain drug and F4 melt dispersion granules (n=6).

Parameters	Plain drug	F4 melt dispersion granules	*t*-test at 0.05 LS
T_{max} (h)	3.00 ± 0.01	2.00 ± 0.01	Significant
C_{max} (ng/ml)	8156.34 ± 587.42	10736.78 ± 182.67	Significant
$AUC_{0\text{-inf}}$ (ng/ml*h)	30956.26 ± 638.68	42764.23 ± 615.39	Significant
$AUMC_{0\text{-inf}}$ (ng/ml*h^2)	120578.46 ± 2978.82	152352.28 ± 3245.47	Significant
MRT (h)	3.89 ± 0.021	3.56 ± 0.028	Not Significant
Relative bioavailability	1.38		

Table 5: Pharmacokinetic parameters of FLB plain drug and F4 melt dispersion granules (Mean ± SD n=6).

Discussion

With the aim to improve the solubility and dissolution rate of water insoluble FLB, the present study was planned to prepare solid dispersions using fusion method. The resulted powder form the combination of fusion method and surface adsorption method was converted into granules, hence they were called as melt dispersion granules. The prepared formulations were evaluated for solubility studies, DSC, angle of repose, *in vitro* dissolution studies, stability studies and *in vivo* bioavailability studies.

Determination of aqueous solubility of prepared solid dispersion formulations is one of the significant factors, which has the strong influence on the dissolution rate. The solubility of FLB melt dispersion granules was determined in 0.1 N HCl, distilled water and phosphate buffer pH 7.2 and the results indicated that the solubility was increased as the pH of the media increased. The aqueous solubility of the FLB is highly pH-dependent in the physiological range due to its pKa of 4.16. As a weak acid, FLB has a higher solubility in a basic aqueous environment, hence showed highest solubility in 7.2 pH phosphate buffers. Similar type of results observed in FLB solid dispersions using gelucires [2]. Among all the formulations, as increasing the carrier concentration, the FLB solubility was increased at a significant level, but after some level there was no proportional increase in solubility by increasing carrier ratio. Similar kind of results was observed in gliclazide solid dispersions using vitamin E TPGS [15].

All the formulations were evaluated for drug content uniformity and they were found to contain 95-101% w/w of FLB, which was within the pharmacopoeial limits (90-110%). From the preliminary studies to select the adsorbent, lactose was shown good to improve the flowability of solid dispersions when compared to microcrystalline cellulose and dibasic calcium phosphate. Hence in the present study, lactose was selected as the adsorbent to improve the flowability of solid dispersions. From the results of angle of repose F1-F4 formulations required 1 g of lactose to show the good flow properties but F5 and F6 formulations 1 g of lactose is inefficient to improve flowability. They required 1.5-2 g of lactose to show good flowability due to high amount of carrier. Similar kind of results was observed in valsartan melt dispersion granules developed by Chella and Tadikonda [5]. From the DSC studies, a sharp endothermic peak was observed at 116°C in plain drug corresponding to the melting point of FLB, but in case of F4 formulation FLB showed broad peak at 125°C. This indicates the change in crystalline state of FLB and may be converted to amorphous form. This might be one of the reasons to enhance the solubility and dissolution rate of melt dispersed granules.

From the *in vitro* dissolution studies, the order of dissolution was observed as follows; melt dispersion granules>marketed tablets>plain drug (Figure 3) and this was the clear indication of dissolution enhancement in case of melt dispersion granules. The dissolution rate enhancement might be due to combined effect of improved wettability, conversion of crystalline to amorphous form and reduction in drug particle size during the formation of solid dispersions [16,17]. Overall increase in the dissolution performance of the F4 formulation was described with the help of dissolution parameters (Q_{15}, IDR, DE, RDR and MDT) and when compared with plain drug and marketed tablets, all the above parameters were increased in case of F4 formulation. In a study developed by Vemula et al., i.e., formulation of flurbiprofen tablets, similar type of improvement in IDR, DE, RDR was reported [8]. From the stability studies of F4 formulation, *in vitro* dissolution data showed that there was no significant change before and after storage. The calculated similarity factor was found to be 84.58, which is more than 50 indicates similarity between the dissolution profile before and after storage.

From the *in vivo* bioavailability studies, significant difference in the plasma concentration time profile of FLB was observed from F4 melt dispersion granules to plain drug after oral administration was due to the improved aqueous solubility and dissolution rate. C_{max} was improved with F4 melt dispersion granules (10736.78 ± 182.67 ng/ml at 2 h T_{max}) in comparison to plain drug suspension due to improved solubility and dissolution rate and it indicates the significant increase in bioavailability. The AUC and MRT (illustrate the resident time in GIT) of F4 melt dispersion granules were found as 42764.23 ± 615.39 ng-h/ml and 3.56 h respectively and they were improved in comparison to plain drug. In a reported study by Mettu et al., i.e., flurbiprofen fast dissolving tablets, similar type of results were observed [9]. The relative bioavailability was found to be 1.38. From the above results, it was confirmed that the F4 melt dispersion granules showed significant improvement in bioavailability of FLB. To conclude, development of melt dispersion granules using vitamin E TPGS and lactose can be a potential alternative method to enhance not only dissolution rate and bioavailability but also flowability and stability of water-insoluble drugs like FLB.

Conclusion

An effort was made to formulate the flurbiprofen melt dispersion granules by incorporating vitamin E TPGS and lactose using combination of melt dispersion and surface adsorption technologies to enhance the dissolution rate and bioavailability. The improvement in the both dissolution rate and bioavailability was brought with the help of vitamin E TPGS and improved flowability due to lactose addition. The prepared melt dispersion granules were also possesses good stability. The results of the pharmacokinetics proved that the there was a significant improvement of bioavailability in case of F4 formulation when compared to plain drug. Hence it was a prominent approach to enhance the dissolution rate and bioavailability of poorly soluble drugs like flurbiprofen.

Acknowledgement

The authors acknowledge the FDC Limited, Mumbai, India and Dr. Reddy's Labs, Hyderabad, India for gift samples. The authors also thank to Management Chaitanya College of Pharmacy Education and Research for providing facilities.

Declaration of Interest

The authors report no conflicts of interest.

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