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Original Research

Formulation and *In Vitro* Evaluation of Flurbiprofen Fast Dissolving Tablets using Sublimation Method

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Abstract

Formulation of oral fast dissolving tablets is not only to give fast relief but also to overcome difficulty in swallowing tablets and capsules, resulting in non-compliance and effective therapy. Present study is intended to formulate the sublimated fast dissolving tablets of flurbiprofen by incorporating super disintegrating agent. Flurbiprofen is a poorly soluble, highly permeable drug and the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. There are several techniques to enhance the dissolution of poorly soluble drugs, in which the sublimation method is a simple and promising technique among the other techniques. Flurbiprofen fast dissolving tablets were prepared by using direct compression method and were characterized for both pre-compression and post-compression parameters to comply with pharmacopoeial limits. The percent drug release in 15 min (Q_{15}) and initial dissolution rate (IDR) for optimized formulation F6 was 92.38±1.18%, 6.16%/min. These were very much higher compared to conventional tablets (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 F6 and it is increased by 4.5 fold with optimized FDT formulation when compared to conventional tablets. Thus developed fast dissolving tablets by sublimation method may be suitable to give rapid drug delivery and rapid onset of action. Further the efficacy of the developed formulations has to be assessed by pharmacokinetic studies in humans.

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INTRODUCTION

Oral route of drug administration through the conventional dosage forms like tablets have wide acceptance up to 60% of total dosage forms. Tablets are still most popular conventional dosage form existing today because of ease of self administration, compact nature, easy to manufacture and can be delivered in accurate dose (Kuchekar *et al*., 2014; Vemula and Katkum, 2014). Formulation of oral solid dosage forms is convenient for many drugs but they are challenging to formulate if the active substances has poor dissolution rate and low bioavailability. To overcome dissolution problems of tablets of poorly soluble drugs, various techniques have been introduced (Neduri *et al*., 2013; Seager, 1998). One of the dissolution enhancement methods is the sublimation technique, which is most widely used and industry feasible method to formulate fast dissolving tablets. Sublimation has been used to produce fast dissolving tablets with high porosity. A porous matrix is formed by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of sublimation (Hirani *et al*., 2009). Some of the recent research examples on sublimation method are flurbiprofen (Vemula and Reddy, 2015), meclizine hydrochloride (Vangala *et al*., 2014), lovastatin (Neduri *et al*., 2013) and clonazepam (Shirsand *et al*., 2011).

The aim of present study is to improve the dissolution rate of poorly soluble flurbiprofen (FLB) using sublimation method. In the present study, sublimated fast dissolving tablets were prepared using camphor as sublimating agent and studied the effect of concentration of sublimating agents in the presence of crosspovidone. FLB, non-steroidal anti-inflammatory agent used to treat pain and inflammation. It is a white to off-white crystalline powder and practically insoluble in water (Veerareddy and Vemula, 2012). Some of the recent research examples on FLB fast dissolving systems are flurbiprofen fast disintegrating tablets (Vemula and Veerareddy, 2011), flurbiprofen fast dissolving tablets (Mettu and Veerareddy, 2013) and flurbiprofen solid dispersions (Daravath *et al*., 2015).

MATERIALS AND METHODS

Materials

Flurbiprofen was procured as a gift sample from FDC Limited, Mumbai, India. Crosspovidone was gift samples

from Matrix laboratories, Hyderabad, India. All other chemicals used were of analytical grade.

Powder Characterization

Before going to compression, powder mixtures of different formulations were evaluated for angle of repose, bulk density, tapped density and Carr's compressibility index. Angle of repose less than 30° suggests free flowing properties of the material. Standard procedures were followed to determine the above parameters given in Vaskula *et al*., 2012.

Preparation of Sublimated Fast Dissolving Tablets (FDTs)

FDTs were prepared by sublimation method. Flurbiprofen, camphor, crosspovidone and other tabletting excipients were passed through a mesh no 60. The drug was mixed with proper portion of sublimating agent and superdisintegrant. Care should be taken to confirm the proper mixing with drug. Then excipients other than glidant and lubricant were added and mixed in a poly bag for 5-10 min. The obtained blend was lubricated with talc and magnesium stearate for another 5 min and the resultant mixture was directly compressed into tablets with 8 mm round flat punches using 16 station rotary tabletting machine, Cadmach, Ahmedabad, India. Then the tablets were sublimated in hot air oven at 50°C for 30min. The final weight of the tablet was adjusted to 200 mg and the compositions of the tablets were given in Table 1 (Vemula and Vangala, 2014).

Table 1: Formulation of FLB sublimated fast dissolving tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Flurbiprofen	50	50	50	50	50	50	50	50
Camphor	5	10	15	20	5	10	15	20
Crosspovidone	5	5	5	5	10	10	10	10
Sodium lauryl sulphate	2	2	2	2	2	2	2	2
Lactose	90	85	80	75	85	80	75	70
Mannitol	40	40	40	40	40	40	40	40
Aspartame	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4
Magnesium stearate	2	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200	200

Evaluation of Fast Dissolving Tablets

The prepared tablets were studied for their physical properties like weight variation, hardness and friability. For estimating weight variation, 20 tablets of each formulation were weighed using an Electronic weighing balance (AW 120, Shimadzu Corporation, Japan). The strength of tablet is expressed by measuring hardness and friability. The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability was determined on ten tablets in a Roche friabilator (Electrolab, Mumbai, India) for 4 min at 25 rpm. For estimation of drug content, ten tablets were crushed in mortar to get powder; this powder was dissolved in. 0.1N HCl buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 247 nm using UV spectrophotometer. Each measurement was carried out in triplicate and the average drug content was calculated (Vemula and Veerareddy, 2011).

***In Vitro* Disintegration Time and Dispersion Time**

In vitro disintegration time of FDT's was determined by following the procedure described by Gohel et al. Briefly, 10 ml of water at room temperature was taken in a petridish of 10 cm in diameter. The tablet was then carefully placed in the centre of petridish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in triplicates. *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of pH 6.8 buffer. Three tablets from each formulation were randomly selected and in vitro dispersion time is expressed in sec (Gohel *et al*., 2004).

Wetting time and Water Absorption Ratio (R)

Wetting time was determined as described in the literature elsewhere. Briefly, two circular tissue papers were placed in a Petri dish of 10 cm diameter. Ten ml of water containing 0.5 (% w/v) of phenol red was added to the petridish. The dye solution was used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of the paper in the petridish at room temperature. The time required for water to reach the upper surface of tablet and to completely wet them was noted as wetting time. Wetting time was recorded using stop watch and the measurements were carried out in triplicates. 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 (Bi *et al*., 1996).

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

***In Vitro* Dissolution Study**

Drug release from prepared tablets was carried out using USP XXIV Type II dissolution apparatus at 50 rpm and 37±0.5 °C temperature using 0.1N HCl buffer. An aliquot of 5 ml was collected at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered through 0.45 µm membrane filters (Millipore, USA) and analyzed at 247 nm using UV-Visible spectrophotometer.

Calculation of Dissolution Parameters

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 and

expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time (15). Relative dissolution rate (RDR) is the ratio between amounts of drug dissolved from optimized from the conventional formulations at 15 min (Vemula and Veerareddy, 2011).

RESULTS AND DISCUSSION

Powder Characterization

The bulk density and tapped density values ranged from 0.291 to 0.332 and 0.354 to 0.412 respectively (Table 2). The results of angle of repose and compressibility index (%) ranged from 25.12±1.13 to 30.65±1.35 and 17.79 to 21.64 respectively. As the angle of repose is a characteristic of the internal friction or cohesion of the particles ,the value of the angle of repose will be high if the powder is cohesive and low if the powder is non cohesive. The results of angle of repose (<40) and compressibility index (<22) indicates fair to passable flow properties of the powder mixture. Finally, all the formulations proven to be acceptably flowing according to either the angle of repose and Carr's index were compressed into tablets and subjected for further.

Table 2: Characterization of powder mixture

Formulation	Angle of Repose* (^{0})	Bulk density (g/cc)	Tapped Bulk density (g/cc)	Carr's index (%)
F1	29.56±1.86	0.315	0.402	21.64
F2	29.56±1.46	0.323	0.398	18.84
F3	25.12±1.13	0.291	0.354	17.79
F4	29.12±1.24	0.321	0.402	20.14
F5	28.31±1.18	0.322	0.403	19.74
F6	27.11±1.14	0.323	0.403	19.74
F7	29.13±1.26	0.302	0.378	20.10
F8	30.65±1.35	0.332	0.412	19.41

* All values represent mean ± standard deviation, n=6

Evaluation of Fast Dissolving Tablets

The physical properties of Flurbiprofen FDTs are given in Table 3 and 4. In weight variation test, the pharmacopoeial limit for the tablets of not more than 7.5% of the average weight. The average percentage deviation of all tablet formulations was found to be within the above mentioned limit and hence all formulations passed the uniformity of weight as per Indian Pharmacopoeia standards. The hardness of the tablets was found to be in the range of 2.9±0.12 to 3.4±0.36 kg/cm^2. Another measure of tablets strength is friability. Conventional compressed tablets that loss less than 1% of their weight are generally considered acceptable. The percentage friability for all formulations was below 0.5 %, indicating that the friability is within the prescribed limits. The tablets were found to contain 97.24±1.54 99.92±0.34 % of the labelled amount indicating uniformity of drug content.

Table 3: Physical evaluation of FLB FDTs using sublimation method

Formulation	Weight variation*(mg)	Hardness** (kg/cm^2)	Friability (%)	Drug content uniformity*** (%)
F1	204.56±0.64	2.9±0.12	0.31	99.42±0.21
F2	199.92±0.73	3.1±0.22	0.34	99.92±0.34
F3	201.34±1.06	2.8±0.26	0.35	98.63±1.05
F4	199.76±0.46	3.4±0.36	0.36	99.82±0.86
F5	202.52±0.24	3.2±0.32	0.28	97.24±1.54
F6	204.34±0.52	3.1±0.21	0.32	98.48±0.48
F7	206.16±0.64	3.4±0.22	0.38	97.64±1.61
F8	198.34±1.12	3.3±0.52	0.29	98.42±0.34

* All values represent mean ± standard deviation, n=20; ** n=6; *** n=3

Table 4: Evaluation of FLB FDTs using sublimation method

Formulation	*In vitro* Disintegration Time* (sec)	*In vitro* Dispersion Time* (sec)	Wetting Time* (sec)	Water Absorption Ratio*	Q_{15}*
F1	58.21 ± 0.49	78.46±0.24	59.86±1.24	46.28 ± 1.68	25.76±0.46
F2	57.62 ± 0.24	76.31±0.56	58.32±1.24	43.28 ± 1.37	31.37±0.32
F3	59.24 ± 0.32	74.42±0.45	56.45±1.32	44.56 ± 1.52	35.92±0.54
F4	52.18 ± 0.53	73.48±0.62	54.28±1.68	43.16± 1.92	59.48±0.86
F5	39.68 ± 0.46	69.34±0.56	36.42±1.32	44.26± 1.74	65.28±1.04
F6	34.56 ± 0.62	68.45±0.76	34.63±1.46	42.22 ± 1.61	92.38±1.18
F7	34.74 ± 0.41	67.56±0.46	32.12±1.14	41.45 ± 1.43	89.74±0.96
F8	37.42 ± 0.38	62.76±0.62	31.63±1.24	44.28 ± 1.22	92.64±0.25

* All results represent avg ± SD, n=3

The disintegration time of all formulations was found in the range of 34.56 ± 0.62 to 58.21 ± 0.49 sec. *In vitro* dispersion time of formulated tablets was found in the range of 62.76±0.62 to 78.46±0.24 sec. 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. The rapid wetting process in almost all formulations may be due to ability of swelling and also capacity of water absorption. The wetting time of formulated tablets was found in the range of 31.63±1.24 to 59.86±1.24 sec and water absorption ratio was 41.45±1.43 to 46.28±1.68.

In Vitro Dissolution Study

The cumulative mean percent of Flurbiprofen released from FDT's containing varying amounts of sublimating agents (from F1 to F8) was found to vary from 25.76±0.46 to 92.64±0.25 in 15 min (Figure 1 and 2). This indicates the fast release of drug is observed from above formulations when compared to conventional tablets (56.24±0.92 % drug release in 60 min). From above dissolution studies, the optimized formulation F6 showed the 99.89±1.32 drug release in the 30 min where as the conventional Flurbiprofen tablets prepared by similar manner. Thus the formulation F6 containing 10% camphor as the sublimating agent and 10% crosspovidone was considered better among other formulations to produce fast release of the Flurbiprofen. This can be well correlated with the evaluation parameter disintegration time which was very lower for the F6 formulation.

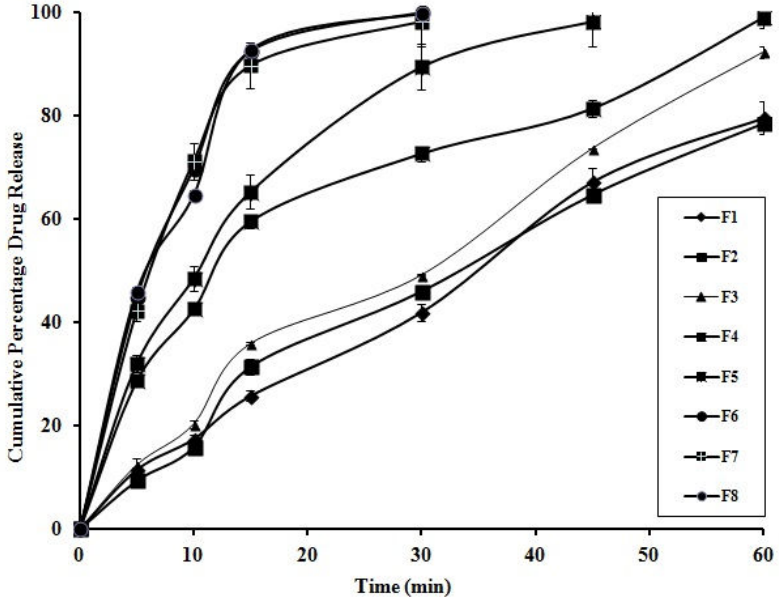

Figure 1: Drug release profile from FLB sublimated fast dissolving tablets (n=3)

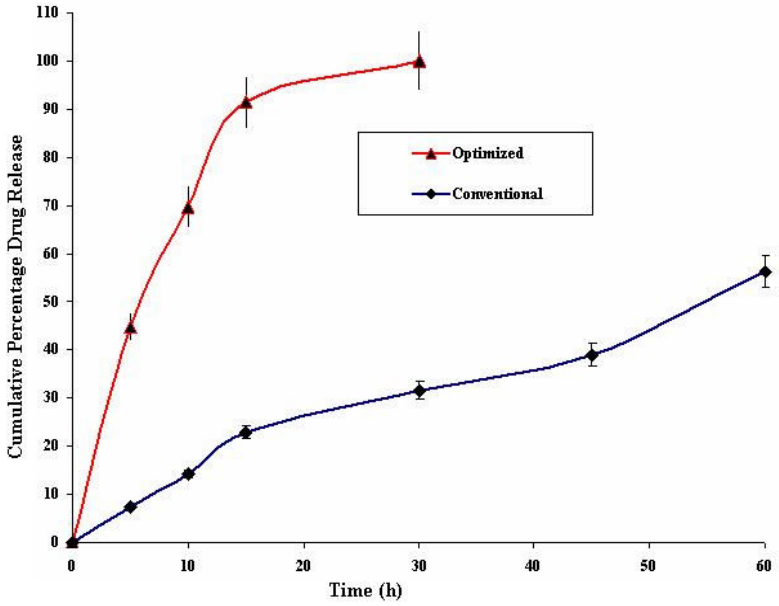

Figure 2: Comparison of drug release from FLB optimized and conventional tablets (n=3)

Calculation of Dissolution Parameters

The percent drug release in 15 min (Q_{15}) and initial dissolution rate (IDR) for optimized formulation F6 was 92.38±1.18%, 6.16%/min. These were very much higher compared to conventional tablets (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 F6 and it is increased by 4.5 fold with optimized FDT formulation when compared to conventional tablets (Table 5). 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 solubility of drug.

Table 5: Dissolution Parameters of optimized and conventional FLB formulations

Formulation	(Q_{15})*	IDR (%/min)	DE	RDR
Optimized (F6)	92.38±1.18	6.16	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.
* All values represent mean ± standard deviation, n=3

CONCLUSIONS

An attempt was made to develop the fast dissolving tablets of Flurbiprofen by sublimation method to achieve fast dissolving effect and to enhance the bioavailability. Flurbiprofen fast dissolving tablets were successfully formulated by employing direct compression method and found to show the significant level of drug release. From the *in vitro* dissolution studies the formulations, F6 was found to be better formulation that showed fast drug release (92% in 15 min) when compared to conventional formulation. Further the efficacy of the developed formulations has to be assessed by pharmacokinetic studies in humans. In conclusion, development of fast dissolving tablets using sublimation method is able to enhance the dissolution rate and there by rapid onset of action to treat pain and inflammation.

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Conflict of Interest

The authors report no conflicts of interest.

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