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Article

Development of fast dissolving tablets of flurbiprofen by sublimation method and its *in vitro* evaluation

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Flurbiprofen belongs to Biopharmaceutical Classification System (BCS) class II drugs which are poorly soluble in water. The objective of present research work was to prepare fast dissolving tablets of Flurbiprofen using varying concentrations of three different sublimating agents to improve the dissolution rate. Seven formulations were prepared containing different concentrations of camphor, ammonium bicarbonate and thymol as sublimating agent along with primogel as a superdisintegrant. Tablets were manufactured by direct compression method. The prepared tablets were evaluated for pre-compression and post-compression parameters result, For all formulations result was within official limits. FTIR studies revealed that there were no interactions between the drug and the excipients used. From in vitro drug release studies it was concluded that the formulations F6 and F7 containing 10% and 15% of thymol showed fast drug release of 100.00% and 100.84% respectively in 30 minutes. Formulations containing camphor (F2 & F3) and ammonium bicarbonate (F4 & F5) as sublimating agents showed a drug release of less than 80%, while the control formulation F1 having no sublimating agent showed 49.14% of drug release in 30 minutes. Thus thymol can successfully be used to formulate fast dissolving tablets of flurbiprofen by sublimation method with much better dissolution profile.

Keywords: Flurbiprofen/dissolution. Fast dissolving tablets. Drug release. Sublimating agent. Superdisintegrant.

INTRODUCTION

Most appropriate route for drug administration is oral route because of versatility, simplicity of intake and most importantly patient compliance. Fast dissolving tablets are acquiring eminence as modern system of drug delivery because disintegration time of such formulations is within seconds to minutes (El-Enin, 2014). Fast dissolving tablets are very beneficial in administration of drugs to children; bedridden patients, in patients having dysphagia, stroke, thyroid disorder, Parkinson's diseases and multiple sclerosis, patients with nausea, vomiting and motion sickness leading to improved patient compliance (Kuchekar, Badhan, Mahajan, 2003).Rate of drug dissolution can be enhanced by different methods which include Direct compression, Wet granulation, Molding, Spray drying, Freeze drying, Lyophilisation and Sublimation (Mettu, Veerareddy, 2013; Nagar *et al*., 2011).

The main objective of preparation of Fast Dissolving Tablets (FDT's) is to prepare a porous matrix of tablets. In sublimation technique for the preparation of such a porous structure various highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane, thymol and phthalic anhydride etc are incorporated in the formulation. Different solvents can also be used for formation of porous matrix, these solvents include cyclohexane, benzene and many others (Goel *et al*., 2008). In this study sublimation technique was employed for designing seven formulations of Flurbiprofen FDT's by use of varying proportions of camphor, ammonium bicarbonate and thymol as sublimating agents.

MATERIAL AND METHODS

Flurbiprofen, thymol, camphor, ammonium bicarbonate were received as a gift from Medizan

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Laboratories and all the other ingredients used were of analytical grade.

Manufacturing of the tablets

Seven formulations (**F1, F2, F3, F4, F5, F6 and F7**) of Flurbiprofen (FLB) tablets were designed in such a way that F1 was control containing no sublimating agent. Formulation F2 and F3 contained 10% and 15% of camphor respectively as sublimating agent, F4 and F5 contained 10% and 15% of ammonium bicarbonate, while F6 and F7 contained 10% and 15% of thymol as sublimating agent.

Accurately weighed quantity of each excipient was mixed except magnesium stearate and talcum and passed through sieve #60. After sufficient mixing accurately weighed quantity of magnesium stearate and talcum were added for lubrication (Vemula, Neduri, 2015). The compositions of the formulations are presented in Table I.

After this, powder mixture of each formulation was evaluated for angle of repose, bulk density, tapped density. The fixed funnel method was employed to measure the angle of repose (θ) and it was calculated using the following formula:

$$Tan\ \theta = h/r$$

where, θ is angle of repose, h is height of the cone, and r is radius of the cone base.

Powder was mixed properly and approximately 2 g of finely mixed powder was added in a funnel which was then set in such a way that lower tip of funnel slightly touches the peak of powder heap. Funnel was set on plane surface and powder was passed freely through it. Measurement of diameter was then done and calculations were done according to above equation (Neduri, Bontha, Vemula, 2013). Bulk density was measured by taking 2 g of properly mixed powder of each formulation into 10 mL of graduated measuring cylinder and powder volume was observed (Neduri, Bontha, Vemula, 2013). For measuring tapped density cylinder was tapped on a hard surface after every 2 seconds and this procedure was repeated until no change in volume was observed. Final volume of powder was then measured. The compressibility index was determined from the bulk and tapped densities and was calculated using the following formula:

Compressibility index= (Tapped Density-Bulk density)/ Tapped Density x 100

After pre-compression studies the powder blend of each formulation was compressed using compression machine ZP 17 with punch size of 12 mm**.** Finally the prepared tablets (except F1) were heated in a hot air oven at 60 °C for 2 hours for removing sublimating agent until constant weight of tablet was achieved.

Post-compression parameters of the tablets

The prepared tablets were studied for post compression parameters like weight variation, hardness and friability. For estimating weight variation, 20 tablets of each formulation were weighed using an analytical weighing balance (Shimadzu, UX 420H). The strength of tablet is expressed by measuring hardness and friability. The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability of ten tablets was determined using Roche friabilator for 4 min at 25 rpm.

Disintegration time

It was calculated by the use of USP disintegration test apparatus. This apparatus consists of a basket rack containing 6-open-ended glass tubes held in a vertical position. A number 10-mesh stainless steel wire screen is attached to the bottom. To test for disintegration time, one tablet from each formulation was individually added into the basket of disintegration apparatus and temperature was set at 37+ 2 °C. Finally time required for complete disintegration was recorded (Kumar *et al*., 2009).

Wetting time and water absorption ratio

One tablet selected from each formulation was placed in a Petri plate with internal diameter of 10 cm, having circular tissue paper folded twice. 0.5% (w/v) of phenol red was added in 10mL of water and this solution was then poured into petri plate and after complete wetting, time was noted using stop watch. For determination of water absorption ratio same test was conducted without using phenol red. Calculation of Water absorption ratio (R) was done according to formula given below (Vemula, Reddy, 2015).

$$R = W_a\text{-}W_b/W_b \times 100$$

W_a represent weight of tablet after wetting, while W_b represent weight of tablet before wetting.

Dispersion time

From each formulation one tablet was selected

randomLy and time in which the tablet gets dispersed entirely was noted. For this purpose 10 mL of water was added in a glass beaker and tablet was added into it. Finally dispersion time was observed and noted using stop watch. The results were recorded in triplicates (Jadhav *et al*., 2011).

Analysis of drug content

For preparation of sample solution 10 tablets from each formulation were randomLy selected and crushed into fine powder by using pestle and mortar. This fine powder blend equivalent to 100 mg of flurbiprofen was then added in 100 mL of 0.1N NaOH and sonicated for 30 minutes. After filtration determination of drug content was done with UV spectrophotometer at 247 nm (Javed *et al*., 2013).

In vitro dissolution study

Flurbiprofin dissolution study was carried out using dissolution type II apparatus. This test was conducted for 45 minutes in 900 mL of 0.1 N HCl at 37±0.5 °C and 50 rpm. In vitro release was determined by collecting 5 mL of sample after 0, 5, 10, 15, 20, 25, 30, 35, 40, 45 minutes and replacing with fresh media. These samples were analysed by UV-visible spectrophotometer at 247nm (Valleri *et al*., 2004).

Kinetics of drug release

For determination of kinetics of drug release for each formulation of FDTs, Zero-order, First-order, Higuchi's, Hixson & Crowell and Korsemeyer Peppas equations were applied on data (Neau *et al*., 1999; Makhija, Vavia, 2002).

Statistical analysis of data

For determination of significant difference in drug release kinetics of different formulations statistical tests including ANOVA and t-test were applied.

Fourier transform infrared spectroscopy (FTIR)

Infrared spectroscopy of pure FLB, active ingredient plus excipients blend of all the formulations was carried out using FTIR spectrophotometer. The spectra were scanned over a frequency range of 3500 to 1000 cm^{-1} (Mettu, Veerareddy, 2013).

Stability studies

For assessment of stability of active and final formulations, ICH guidelines were followed and stability studies were carried out accordingly. All the samples were carefully packed in aluminium foil and kept in humidity chamber set at temperature and humidity conditions of 40±2 °C and 75±5% RH respectively for one month (Vemula, Neduri, 2015).

RESULTS AND DISCUSSION

Pre-compression parameters

Each formulation blend of drug and excipients

TABLE I - Composition of formulations prepared by sublimation technique

Excipients (mg/tab)	Formulations						
	F1	F2	F3	F4	F5	F6	F7
Flurbiprofen	100	100	100	100	100	100	100
Microcrystalline cellulose(102)	243	198	175.5	198	175.5	198	175.5
Lactose SD	35	35	35	35	35	35	35
Primogel	20	20	20	20	20	20	20
Colloidal silicon dioxide	4	4	4	4	4	4	4
Thymol	-	-	-	-	-	45	67.5
Camphor	-	45	67.5	-	-	-	-
Ammonium bicarbonate	-	-	-	45	67.5	-	-
Mannitol	30	30	30	30	30	30	30
Talcum	8	8	8	8	8	8	8
Magnesium stearate	10	10	10	10	10	10	10
Net weight	450	450	450	450	450	450	450

prepared were evaluated for angle of repose, bulk density, tapped density and compressibility index. Bulk density was found in the range of **0.35-0.45 g/mL** and tapped density between **0.39-0.50 g/mL.** Angle of repose was also evaluated which was between **24.36** and **30.50.** The powder blends of all the formulations had compressibility index between **10.01** and **13.32** as shown in Table II. The results indicated that the powder blends possessed ideal properties required to be produced by direct compression method.

Post-compression parameters

Flurbiprofen fast dissolving tablets were prepared in seven formulations (F1 was control having no sublimating agent) by compressing powder blend using direct compression technique.The data obtained from post-compression parameters such as thickness, hardness, friability, weight variation, amount of drug content, wetting time, water absorption ratio and disintegration time are shown in Table III.

Tablet hardness values lied between **5.0 ± 0.21 to 5.4 ± 0.33 kg/cm²(acceptance range = 5-8 kg/cm²)** for all the formulations indicating good mechanical strength with an ability to withstand physical and mechanical stress conditions while handling. Thickness value of tablets lied between **3.20 ± 0.05 to 3.24 ± 0.06 mm (acceptance range = ± 5%).**In all the formulations the friability values were less than 1% and met the Pharmacopoeial limits. The loss of percentage of weight of all the formulations in friability was **0.41 ± 0.02 to0.58 ± 0.06** which was well below the allowed official limits.

Wetting time of tablets prepared from sublimation technique ranged from **51 ± 0.49 to 56 ± 0.85 seconds**. Dispersion time values were found in the range from **54 ± 0.24 to 61 ±0.47 seconds**. Results of disintegration test lied between **40 ± 0.79 to 46 ± 0.25 seconds (acceptable disintegration time standards are 5 minutes).**The results

TABLE II - Pre-compression parameters of the formulations

Formulations	Bulk Density (g/mL) ± S.D (n=3)	Tapped Density (g/mL) ± S.D (n=3)	Hausner's Ratio ± S.D (n=3)	Angle of Repose ± S.D (n=3)	Compressibility Index (%) ± S.D (n=3)
F 1	0.43 ± 0.025	0.49 ± 0.042	1.12 ± 0.037	26.66 ± 0.73	11.51 ± 0.76
F 2	0.36 ± 0.033	0.42 ± 0.074	1.14 ± 0.038	25.10 ± 0.71	13.32 ± 0.79
F 3	0.35 ± 0.033	0.39 ± 0.012	1.10 ± 0.031	24.36 ± 0.68	10.01 ± 0.42
F 4	0.45 ± 0.041	0.51 ± 0.017	1.18 ± 0.046	25.24 ± 0.70	12.85 ± 0.62
F 5	0.37 ± 0.022	0.42 ± 0.074	1.15 ± 0.039	30.31 ±0.60	11.08 ± 0.42
F 6	0.45 ±0.041	0.51 ± 0.017	1.15 ± 0.039	29.89 ± 0.61	12.87 ± 0.68
F7	0.45 ± 0.041	0.50 ± 0.017	1.10 ± 0.031	30.50 ± 0.60	10.94 ± 0.43

TABLE III - Post compression parameters of the formulations

Sr.	Parameters	F 1	F 2	F 3	F 4	F 5	F6	F7
1	Hardness (kg/cm²) ± SD, n=3	5.4 ± 0.33	5.2 ± 0.29	5.0 ± 0.21	5.1 ± 0.14	5.0 ± 0.20	5.1 ± 0.14	5.0 ± 0.24
2	Thickness (mm) ± SD, n=3	3.21 ±0.04	3.23 ± 0.03	3.23 ± 0.05	3.20 ± 0.09	3.20 ± 0.05	3.24 ± 0.06	3.21 ± 0.09
3	Friability (%w/w) ± SD, n=3	0.58 ± 0.06	0.41± 0.04	0.43 ± 0.08	0.41± 0.02	0.48 ± 0.04	0.43 ± 0.02	0.51 ± 0.09
4	Disintegration Time (Sec) ± SD, n=3	46 ± 0.25	43 ± 0.21	45 ± 0.49	43 ± 0.57	45 ± 0.40	40 ± 0.79	41 ± 0.73
5	Wetting Time (Sec) ± SD, n=3	56 ± 0.85	55 ± 0.11	56 ± 0.14	54 ± 0.36	51 ± 0.49	56 ± 0.50	54± 0.32
6	Dispersion Time (Sec) ± SD, n=3	54 ± 0.55	58 ± 0.91	54 ± 0.45	61 ± 0.21	60 ± 0.26	61 ± 0.47	54 ± 0.24
7	Drug Content	100.03%	99.97%	100.03%	99.99%	99.98%	99.99%	100.02%

of wetting time and disintegration time of all the tablets were found to be within the prescribed limits and satisfied the criteria of fast dissolving tablets. All the formulations possessed acceptable hardness, friability, wetting time and disintegration time which is an absolute requirement for any fast dissolving tablet.

From the dissolution studies, cumulative percentage of drug release versus time was evaluated as presented in Figure 1. Figure 1 represents the percentage release of all the formulations against time. It also reflects that the formulations F6 and F7 containing 45 mg and 67.5 mg of thymol respectively showed fast drug release of 100.00% and 100.84% respectively in 30 minutes as compared with formulations containing other sublimating agents. Among all the formulations, F6 and F7 tablets showed complete drug release within 30 minutes and rapid dissolution. The possible reasons and mechanisms for increased dissolution rates are formation of porous structure on the surface of tablet due to sublimation and the presence of superdisintegrants which enhance the water permeation (wicking action) into the tablet, which leads to a prompt wetting action, short disintegration time and finally causes the fast dissolution rate. It was observed that as the concentration of sublimating agents was increased the drug release also increased, because as the concentration of sublimating agent increases, there will be more number of pores formed in the tablet, because of which water can enter and get absorbed in more quantity, which will lead to rapid disintegration.

Drug release rates obtained for the formulations were subjected for kinetic treatment to know the order of drug release rates. Values of the drug release were attempted to fit into various mathematical models to observe the mechanism as showed in Table IV. The correlation coefficient values were obtained for all the five models. Model fitting plots of the optimized formulations best suited Krosmeyers-Peppas release kinetics as shown in Figure 2- Figure 6.

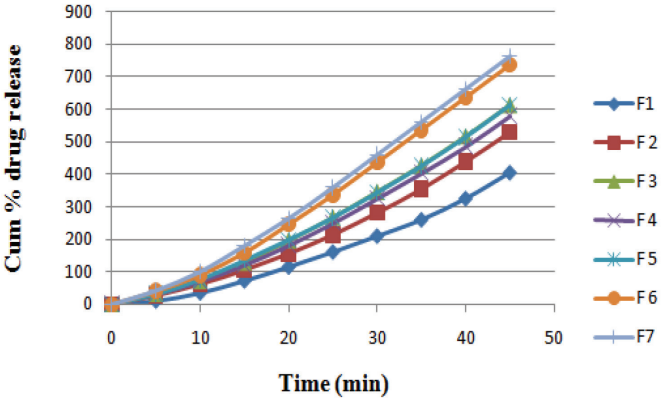

FIGURE 2 - Zero order release kinetics plot.

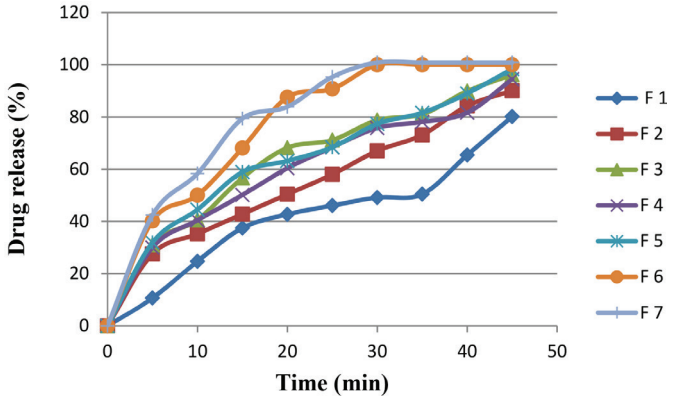

FIGURE 1 - Drug release (%) of formulations versus time (min).

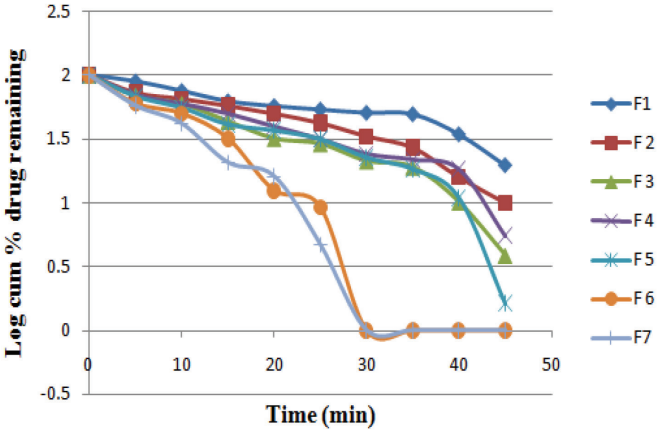

FIGURE 3 - First order release kinetics plot.

TABLE IV - Drug release kinetics (R^2 values of formulations)

Formulations	F1	F2	F3	F4	F5	F6	F7
Zero order	0.8824	0.8125	0.5329	0.5900	0.5053	0.0225	-0.5311
First order	0.9176	0.9403	0.9707	0.9582	0.9451	0.9474	0.9156
Higuchi plots	0.8594	0.9556	0.9857	0.9869	0.9893	0.8883	0.8095
Hixon and Crowell	0.9180	0.9388	0.9375	0.9216	0.9034	0.9666	0.9719
Korsemeyer peppas plots	0.9328	0.9834	0.9858	0.9882	0.9893	0.9159	0.9741

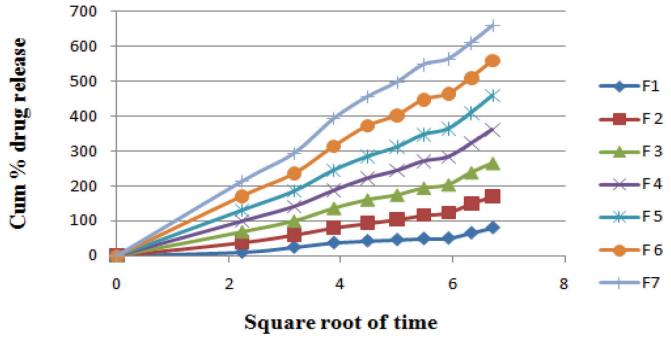

FIGURE 4 - Higuchi model plot.

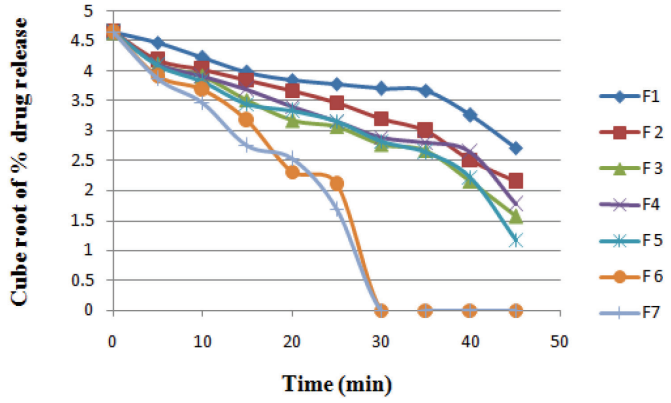

FIGURE 5 Hixon-Crowell model plot.

For the determination of difference of the drug release between the control formulation and the other six formulations t-test and ANOVA were applied on data.

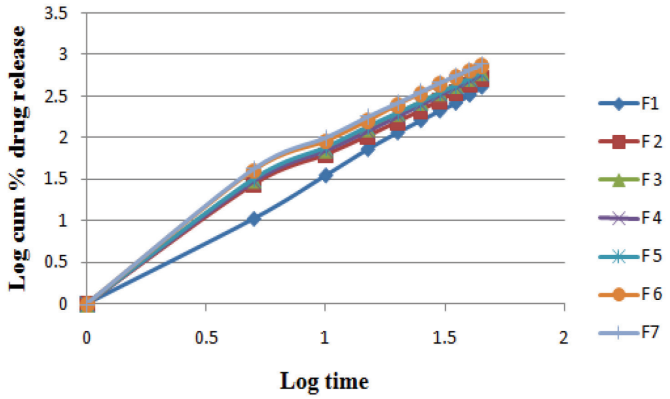

FIGURE 6 - Krosmeyers-Peppas model plot.

ANOVA results are shown in Table V. If F value is greater than F_{crit} value it shows significant difference in drug release profile of different formulations. According to results presented in Table V. $F>F_{crit}$ F value 3.4814 is greater than F_{crit} value 2.2655. Therefore results confirm that there is significant difference in drug release of the seven formulations.

t-Test was also performed and results revealed that t Stat < t Critical two-tail it means that there is significant difference between the drug release kinetics of the optimized formulations prepared by sublimation technique and the control formulation.

The FT-IR studies revealed that flurbiprofen is compatible with the excipients used in the formulation. There were no extra peaks observed in the IR spectrum. The IR absorption band in cm^{-1} of the drug and excipients

TABLE V - Results of one way ANOVA

Anova: Single Factor						
SUMMARY						
Groups	Count	Sum	Average	Variance		
Row 1	9	406.64	45.18222	418.9677		
Row 2	9	528.34	58.70444	469.3118		
Row 3	9	613.41	68.15667	476.8833		
Row 4	9	579.31	64.36778	438.8329		
Row 5	9	613.19	68.13222	449.5777		
Row 6	9	736.6	81.84444	545.937		
Row 7	9	759.27	84.36333	445.0354		
ANOVA						
Source of Variation	SS	Df	MS	F	P-value	F crit
Between Groups	9682.063987	6	1613.677	3.481455	0.005388	2.265567
Within Groups	25956.36691	56	463.5066			
Total	35638.4309	62				

was found to be similar. This established that the drug flurbiprofen and all the excipients used in the study showed no interaction and indicated that they were compatible with each other.

FTIR spectrum of pure FLB show the characteristic peaks shown below: (Sohail *et al*., 2014)

TABLE VI - Characteristic peaks of flurbiprofen

Characteristic peaks	Wavelength (cm^{-1})
Sharp peak representing (C=O)	1694.9
Peak representing stretching of (C-F)	1215.6
Characteristic broad peak of flurbiprofen due to hydrogen bonding	2,500 – 3,300

Visual representation of FTIR spectra of active and powder mixture of best formulations presented in Figure 7- Figure 9.

Stability studies were carried out on optimized formulations F6 and F7. Formulations were stored at 40°C ± 2 °C /75 ± 5% RH for 30 days. No significant changes were found during study period. Thus the formulations were found to be stable.

CONCLUSION

In conclusion, FDTs of Flurbiprofen were developed that had sufficient mechanical integrity, and uniformity of content. The FDTs were prepared by direct compression method using sublimation technique. All tablets had hardness in the range 5.0–5.4 kg/cm^2 and friability less than 1%. Weight variation and drug content of all formulations were within official limits. In vitro disintegration tests and in vitro drug release studies of FDTs tablets showed that best formulations F6 and F7 containing 10% and 15% of Thymol as sublimating agent disintegrate within seconds and the total amount of drug was released within 30 minutes while none of the other formulations showed complete release of the drug within specified time. Hence, the optimized formulations F6 and F7 can be effectively used for the treatment of pain, arthritis and other inflammatory conditions.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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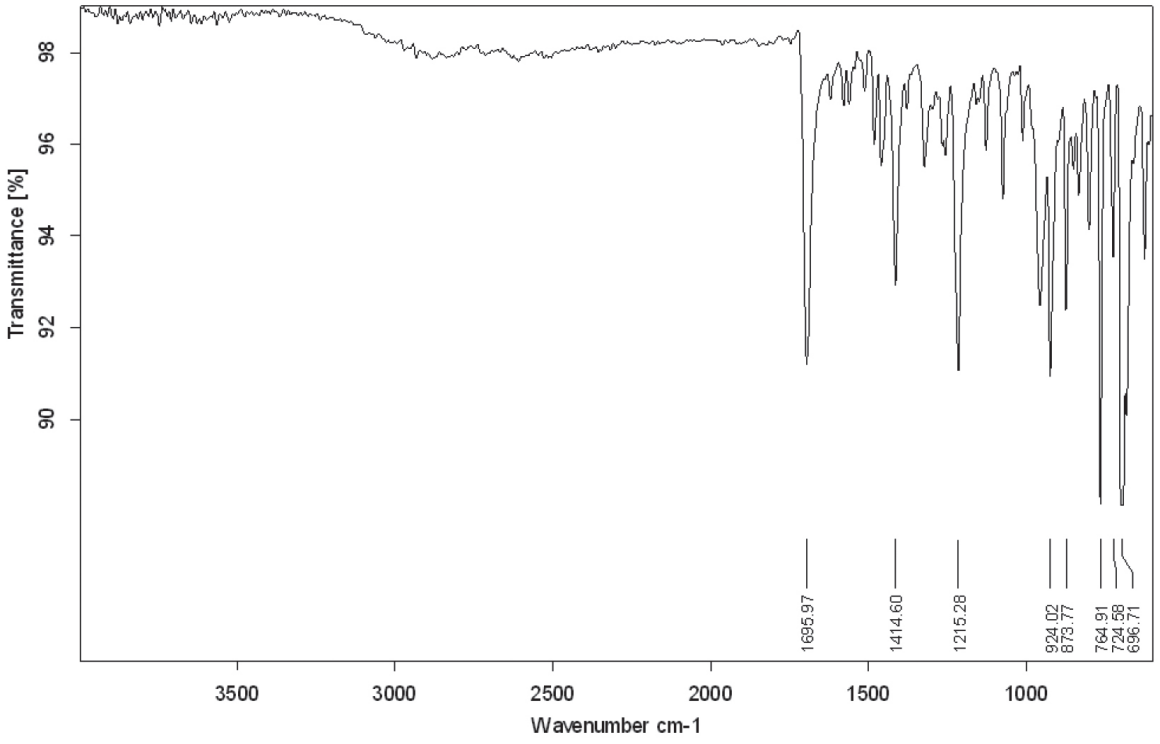

FIGURE 7 - FTIR spectra of flurbiprofen.

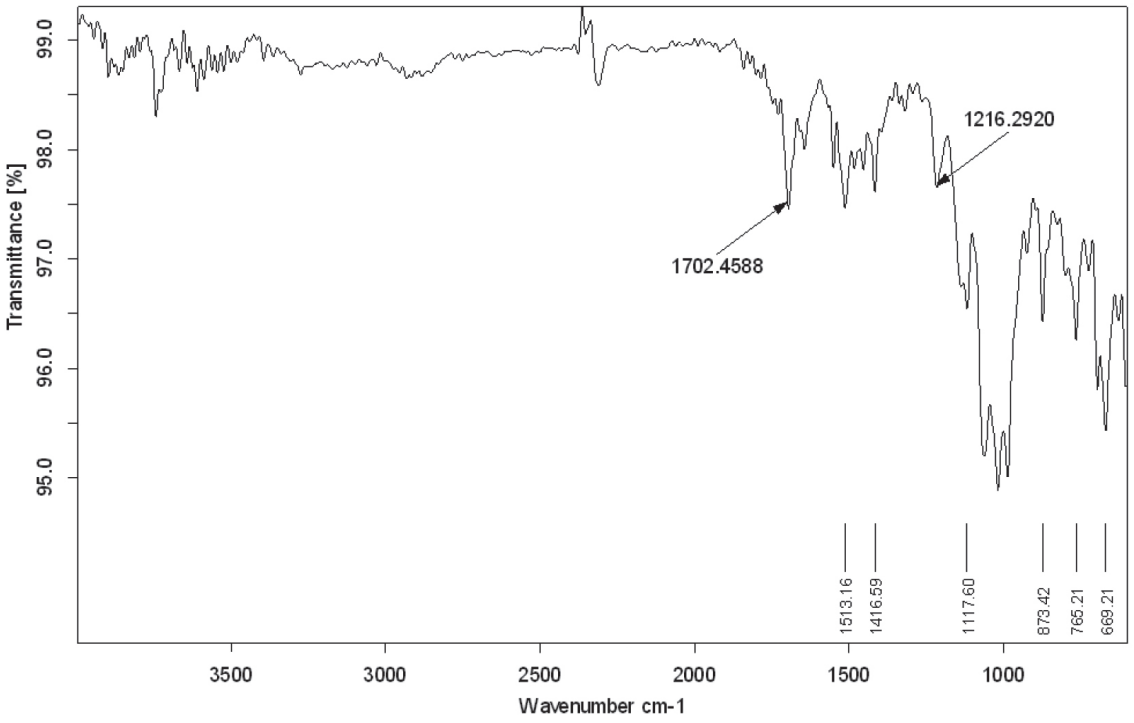

FIGURE 8 - FTIR spectra of formulation F6.

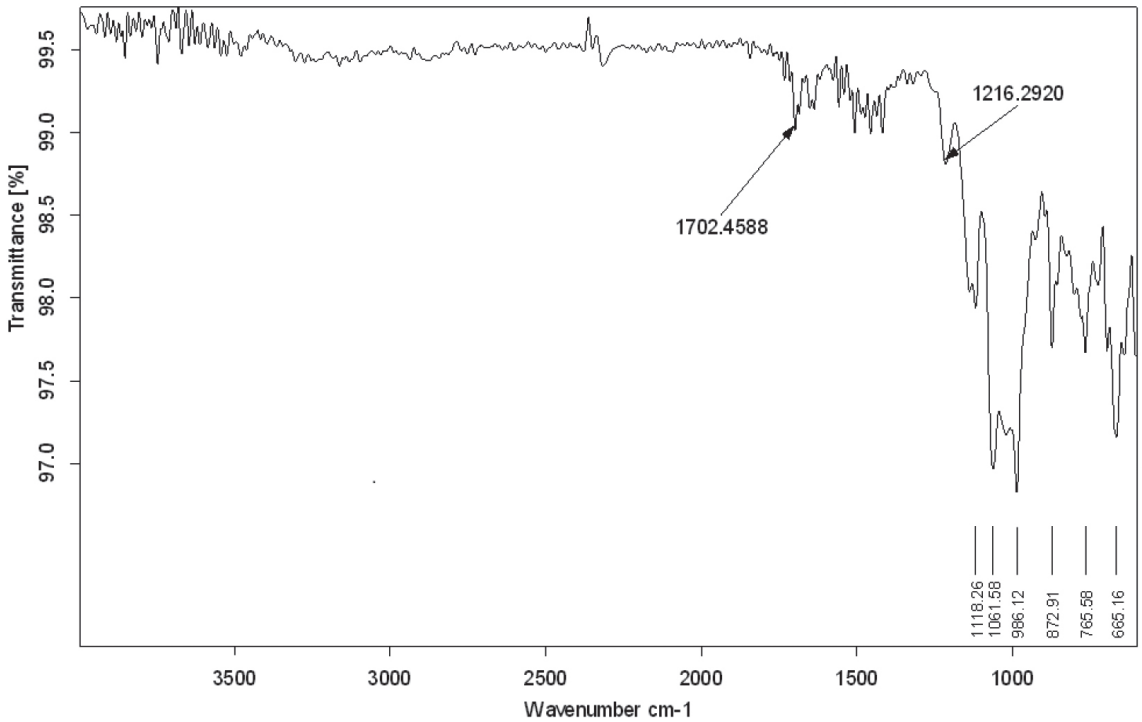

FIGURE 9 - FTIR spectra of formulation F7.

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