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Formulation and Evaluation of Ketotifen Fumarate Fast Disintegrating Sublingual Tablets

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Abstract

The aim of this study was to formulate KF fast disintegrating sublingual tablets (FDSLTs). KF undergoes first pass metabolism in liver, which has oral bioavailability of only 50% of the administrated dose. Sublingual dosage form bypasses the metabolism of KF in liver and offers a fast relieve of asthma. To achieve this goal, superdisintegrants and diluents were evaluated for their effect on the disintegration behavior of KF tablets. Full factorial design (24) was applied for a screening study in which four factors were used at two levels (low and high). The four factors, were the type of disintegrants either Ac-di-sol or Explotab, the concentration of each disintegrant (either 3% or 5% w/w), the binder either Avicel PH101 or PEG6000 and finally the diluent was either spray dried lactose or granular mannitol. The weight variation, content uniformity, friability, hardness, disintegration time, and in-vitro dissolution of the prepared formulae were evaluated. Hydroxy propyle betacyclodextrin (2-HP-βCD) was used for increasing the absorption of KF tablets formulae. Solid binary system of KF with betacyclodextrin (2HP--βCD) was prepared in molar ratios of 1:1 of drug to cyclodextrin. The formula F9 containing Ac-di-sol(5%w/w) , Avicel PH101(10%w/w) and granular mannitol as diluent was selected as best formula that has the least disintegration time of 20 seconds and the highest cumulative dissolution percent of 80.28% after the first minute. The relative bioavailability of F9 both with and without the cyclodextrin was compared. Zaditen® tablets were taken as reference standard. The formula F9 showed mean peak plasma concentration Cmax of 25.578±2.65ng/mL, the mean time of peak plasma concentration tmax of 1.167±0.258 h and the AUC (0-∞) of 319.894± 69.13ng.h/mL. However, FC9 that containing the drug in the form of a complex with 2HP-βCD showed Cmax of 30.901±4.963ng/mL, tmax of 1.083±0.186h and AUC (0-∞) of 382.166±55.278ng.h/mL. The results indicate that KF/2-HP-βCD fast disintegrating sublingual tablets may serve as a successful strategy for enhancing the bioavailability of KF drug.

Keywords: Sublingual tablets, Ketotifen Fumarate, 2-HP-βCD, Fast disintegration, Bioavailability.

Introduction

Ketotifen is a non-specific mast cell stabilizer, which can prevent the development of asthmatic conditions by H_1-receptor antagonism, phosphodiestrase inhibition resulting in accumulation of cyclic adenosine mono-phosphate (c AMP) inside the cells, inhibition of the release of inflammatory mediators SRS (slow reacting substance of anaphylaxis) and inhibition of calcium flux in bronchial smooth muscle [2, 3]. Moreover, early treatment with ketotifen limits the need for other anti-asthmatic drugs including steroids [4].

Various techniques can be used to formulate rapidly disintegrating or dissolving tablets of ketotofen fumerates [4]. Direct compression is the easiest way of manufacturing tablets. The biggest advantages are the low manufacturing cost, high mechanical property of the tablets and it is the ideal method for moisture and heat-labile medications [5]. Cyclodextrins and their derivatives have been frequently used to enhance the bioavailability by increasing the drug solubility, dissolution and/or permeability [6]. They also act as penetration enhancers by increasing the drug availability at the surface of biological barrier [7]. Cyclodextrins have also been beneficial in reducing the undesirable properties of drugs, like gastric irritation [8], masking unpleasant tastes or odors [9]. The purpose of this study was to engineer a fast disintegrating sublingual tablets that bypass the hepatic metabolism, improve the patient compliance which are able to enhance the permeability and bioavailability of selected

formulae through complexation with 2-HP-βCD. Evaluation of the complex as an absorption enhancer using six male volunteers and was carried out to compare the bioavailability of the prepared FDSLTs formula with the marked formula (Zaditen® tablets).

Materials and Methods

Materials: Ketotifen fumarate (generously gifted by Memphis Co., Egypt); 2-Hydroxy propyl- ß-cyclodextrin (chemical Co., Milwaukee, WI, USA). Polyethylene glycols 6000 (Fluka AG Buchs SG, Switzerland); Avicel PH 101: microcrystalline cellulose, (FMC Corporation, Pennsylvania, USA); Aerosil 200: colloidal silicon dioxide (Degussa-Huls Ltd., Frankfurt, Germany); Explotab: sodium starch glycolate and Ac-di-sol: crosscarmellose sodium(FMC corporation, Philadelphia ,USA); magnesium stearate, (Prolabo, France); spray dried lactose and granular mannitol (spray-dried NF, Fast Flo; Foremost Farms, Baraboo, WI).

Tablet preparations:

Fast disintegrating sublingual tablets were prepared by direct compression technique. A full factorial design (2^4) was applied for the screening study in which four factors were used at two levels. These factors were the type of superdisintegrants either Ac-di-sol or Explotab, the concentration of superdisintegrants either low (3%w/w) or high (5%w/w), the type of binder either Avicel PH101 or PEG6000 at concentration of (10%w/w) and finally the type of diluent either spray dried lactose or granular mannitol. A combination of magnesium stearate (1% w/w), aspartam (1% w/w) as sweetening agent, mint flavor (0.5% w/w) and Aerosil 200 (2% w/w) which is used as permeabilizing and antistatic glidant were all combined for the preparation of FDSLTs as shown in the table 1. All the ingredients of the sublingual tablets of KF were weighed and mixed in a mortar and pestle, then finally magnesium stearate (1mg) and Aerosil(2mg) were added for a good lubrication characteristics. The blended material was slightly compressed on the flat–faced punch (7mm) using a single punch machine (Erweka type, GmbH, Germany). The total weight of the formula was maintained at 100mg.

Evaluation of the prepared fast disintegrating sublingual tables

All the prepared tablets of formulae from F1 to F16 were evaluated for their weight variations, friability, hardness, drug content, disintegration and dissolution rate and weight variation tests were evaluated using twenty tablets of each formula randomly, and individually weighed. No more than two of the individual tablets deviate from the average weight by more than 5%, and none deviate by more than twice that percentage [10-12]. Friability was tested using friabilator, Pharma test, (Erweka type, GmbH, Germany). Carried out according to British pharmacopoeia (B.P.) [11] while hardness was investigated using Erweka hardness tester (M6d, Drish leuniger, Pharmaton). For the disintegration time test; the tablets were inserted in each of the six cells of the disintegrator, USP Disintegration tester apparatus (Hanson research,USA) ; In this experiment simulated saliva fluid (SSF) pH=6.75 kept at 37 ± 1°C was carried out on the disintegration apparatus and the basket was raised and lowered at a constant frequency of 30±2 cycles/min. The test results were presented as the average of six determinations. For each formula the total time of disintegration was measured [13, 14]. The content of KF in different tablets was determined by accurately weighing ten tablets of each formula individually. Each tablet was crushed and dissolved in methanol (8 mL) that is placed in a volumetric flask(10ml). The solution was filtered, suitably diluted and the drug content was analyzed spectrophotometrically (Shimadzu, UV-1601) at 300nm.

Enhancing the permeability of Selected Ketotifen Fumarate Fast Disintegrating Sublingual tablets via the complexation with 2-HP-βCD:

Only eight formulae out of the sixteen formulae (from F1 to F16), which pass the previous quality control were chosen to forms inclusion complex with 2-HP-βCD in molar ratio (1:1) by precipitation method. The clear solutions of HP-ß-CD in distilled water and KF in ethanol-water (80:20, v/v) solution were mixed at the molar ratios of (1:1). The obtained solution was dried under vacuum at room temperature using a rotary evaporator. The selected formulae were F1, F2, F3, F9, F11, F12, F13 and F16. Tablets were prepared as mentioned before by replacing Ketotofen fumerate with ketotifen fumarate/ 2-HP-βCD complex in a molar ratio of 1:1. All other additives were added to have eight new formulae namely; F_c1, F_c2, F_c3, F_c9, F_c11, F_c12, F_c13 and F_c16 (where **c** refers to complex formation of ketotifen fumarate and 2-HP-βCD). The complex of KF and 2-HP-βCD in (1:1) molar ratio was prepared by coprecipitation method and characterized by differential scanning calorimetry (DSC) and X-ray powder diffractometry (XRD) as reported by our group [15] .

Characterization of ketotifen fumarate/ 2-HP-βCD fast disintegrating sublingual tablet

The prepared KF/2-HP-βCD fast disintegrating sublingual tablets namely; F_c1, F_c2, F_c3, F_c9, F_c11, F_c12, F_c13 and F_c16 were subjected to the following quality control tests: Friability test, Hardness test, Disintegration time and Content uniformity as prescribed before. In addition, to determine the oral disintegration time and in- vitro dissolution studies for 5 minutes for choosing the best formula for bioequivalence study.

In-vivo disintegration time

The in vivo disintegration time of each of the prepared FDSLTs was evaluated in six human volunteers. All volunteers were asked to rinse their mouth with distilled water. Each of the six subjects was given a coded tablet. Tablets were placed under the tongue and immediately the time of the disintegration was recorded. The subjects were asked to spit out the content of the oral cavity after

tablet disintegration and rinse their mouth with distilled water. The swallowing of saliva was prohibited during the test, and saliva was rinsed from the mouth after each measurement. The test results are presented as mean value ± SD.

In-vivo absorption studies

The studies were carried out to compare the pharmacokinetics of KF from a FDSLTs formula (F9 treatment A) and formula (Fc9 treatment B) in comparison to the conventional Zaditen® tablet (Novartispharma , Egypt) and labeled as treatment C. A single dose of ketotifen, fumarate (1.38mg) was given to the volunteers using randomized, single dose, three-way crossover open-label study randomized crossover design (table 2).
Six healthy man volunteers aged between 20 to 40 years (median weight: 75 kg and median height: 183 cm) were chosen. Health status of the volunteers was confirmed by complete medical history, physical examination and laboratory analysis for complete hematological and biochemical examination, all these were carried out at baseline. None of the volunteers had any history of drug or alcohol abuse, nor did they have any acute or chronic gastrointestinal, cardiac, vascular, hepatic or renal disease. The protocol of the study was conducted according to Helsinky agreement protocol and according to the requirements of the ethical committee of the faculty of Medicine , The University of Beni Suef, Beni Suef, Egypt.

The drug was administered orally after fasting overnight and washout period of 1 week. Venous blood samples (5 mL) were collected into heparinized tubes at the following time intervals: 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 24 h after administration of a treatment. Plasma was obtained by centrifugation at 2000 rpm for 10 min and stored at -20ºC until the time of analysis.

Chromatographic conditions

A modified HPLC method of [for the determination of ketotifen fumarate in plasma was adopted [16]. The HPLC apparatus consisted of: Isocratic pump LC-10 AS and a UV/VIS detector SPD-10A connected to a C-R6A Integrator (Shimadzu, Koyoto, Japan). The analytical column was Ponapak C18 HPLC column, 4.6 x 250 I.D mm, particle size 125 ºA (Waters Associates, Ireland). The mobile phase composed of methanol: water in a ratio of 80:20 (V/V) containing triethaylamine (0.2%v/v), with a flow rate of 1 ml. min^{-1}. The system was operated at ambient temperature and the detection wavelength was carried out at 296 nm.

Plasma analysis

One mL of the plasma sample was mixed with acetonitrile (1 mL) and stock solution of the internal standard (1 mL). The mixture was vortexed for 1min and then centrifuged for 10 min at 3000 rpm. The upper layer was separated and transferred to another tube then filtered through 0.45 µm Millipore® filter for analysis with HPLC. Twenty µL of the samples were injected to the column for analysis. The recovery (10-600ng/mL) varied between 91.55 and 100.86%.

Pharmacokinetic analysis

Pharmacokinetic characteristics from plasma data following administration of the two treatments were estimated for each subject using, WinNonlin® (version 1.5, Scientific consulting, Inc., Cary, NC, USA). Non-compartmental analysis was used. C_{max} (ng/mL) and t_{max} (h) were the observed maximal drug concentration and the time needed to reach this concentration respectively. The area under the curve, $AUC_{(0-24)}$ (ng.h/mL) was calculated using the trapezoidal rule from zero time to the last time of the blood sample. The area under the curve from zero to infinity, $AUC_{(0-\infty)}$ (ng.h/mL), was calculated as $AUC_{(0-\infty)} = AUC_{(0-24)} + Ct/k$, where C_t is the last measured concentration at time t, and k is the terminal elimination rate constant estimated by log-linear regression analysis on data visually assessed to be at terminal log-linear phase. Apparent terminal elimination half-life ($t_{1/2}$) was calculated as $t_{1/2} = 0.693/k$. Mean residence time (MRT) was calculated from AUMC/AUC. The relative bioavailability was calculated as (AUC_{test} / $AUC_{standard}$) x100.

Statistical analysis

An analysis of variance (ANOVA) was performed for untransformed data for the pharmacokinetic parameters C_{max}, t_{max}, AUC_{0-24}, and $t_{1/2}$ using the software SPSS 11.0 (SPSS Inc., Chicago, USA) at p-value ($p \leq 0.05$).

Results and Discussion

Evaluation of the fast disintegrating sublingual tablets

Table 3, shows the data obtained from the evaluation of tablets. All the fast disintegrating sublingual KF formulae in the factorial design complied with the compendia standards for the weight variation and content uniformity tests (all tablet formulae were found to conform to pharmacopoeial limit 85% - 115%) of the label claim. The prepared tablets showed a uniformity of diameter and thickness.

Tablet hardness

All the tablets maintained hardness in the range of 4.14 to 7.62 kilograms. The statistical analysis revealed that all factors; superdisintegrant type, superdisintegrant concentration, binder type, and diluent exhibited a significant effect on the hardness of the prepared formulae ($p \leq 0.05$) as shown in figure 1.

Tablet Friability

According to compendial standards of the British pharmacopoeia, the tablets comply with the friability test if the weight loss during the test was less than 1% of the given weight. The tablets should not break or show any capping or cracking during the test. Table

3, shows that the tablets formulated with the different excipients showed low percentage of fines within the acceptable range except for only two formulae, namely F10 (containing 5% Ac-di-sol together with 10%Avical PH101 and lactose) and F14 (containing 5% Explotab together with 10% Avical PH101 and lactose). In addition, formula F4 and F15 had one broken tablet.Although many formulae had high friability values, yet they are still within the permissible limits. It is not surprising to find these percentage weight loss values owing to the nature of the rapidly disintegrating tablets which require certain packaging materials [17] .

In-vitro disintegration test

The shortest disintegration time were observed from F9, F10, F13, and F14 having average disintegration time of 24.13, 34.79, 28.29 and 35.68 seconds, respectively. This might be due to the synergistic effect of both of Avicel PH101 and the higher concentration of the superdisintegrants either Ac -di-sol or Explotab in those formulae (AvicelPH10l works as a disintegrant in concentration of 5-15%). ANOVA test at $p \leq 0.05$ was carried out followed with Fischer's PLSD test (pair-wise least significant difference) to test the significance of the difference between the tested factors and their effects on tablet disintegration time at 95% confidence limits which, found that all factors under study, namely, superdisintegrant type, superdisintegrant concentration, binder types and diluent types had significant effects on the disintegration time of the prepared FDSLTs ($p<0.05$) , the results were graphically illustrated in (figure 2).

In-vitro dissolution studies:

Ideally, physiological conditions at the site of administration should be taken into account when selecting the in-vitro dissolution/release test condition the saliva ordinary maintains the pH of the mouth between 5.6 and 7.6. Therefore, in the dissolution studies, simulated saliva fluid (SSF) that has a pH of 6.8±0.5 was adopted as a dissolution medium [18]. All the examined formulae showed 100% drug dissolution after 5 minutes due to the water solubility of the drug.

Enhancing the permeability of selected ketotifen fumarate fast disintegrating sublingual tablets through the complexation with 2-HP-βCD

The permeability of selected formula can be enhanced through complexation with 2-HP-βCD. Cyclodextrins and their derivatives have been frequently used to enhance the bioavailability by increasing the drug solubility, dissolution and/or permeability [6]. They also act as penetration enhancers by increasing the drug availability at the surface of biological barrier [7]. The physicochemical characterization of KF/2-HP-βCD binary solid systems were proved by differential scanning calorimetry (DSC) and X-ray powder diffractometry (XRD) [6] as illustrated in (figure 3 and 4).

Characterization of KF/ 2-HP-βCD fast disintegrating sublingual tablets

Concerning the content uniformity of the prepared formulae, it was found that the selected formulae were complying with the USP specification for content uniformity where the amount of the drug determined lied within the acceptable range from 98.44% to 102.57 % of the claimed dose. Regarding hardness, friability and disintegration time, there was no significant difference before and after the complexation. All the prepared formulae containing drug complex showed acceptable hardness, friability and *in-vitro* disintegration times less than one minute were subjected to measurement of the buccal disintegration time and *in-vitro* dissolution studies for 5 minutes for choosing the best formula.

Buccal Disintegration Time

The average buccal disintegration time arranged in the following order: $Fc9 > F_c13 > F_c11 > F_c2 > F_c16 > F_c3 > F_c1 > F_c12$.

The percent of ketotifen fumarate within five minutes

The percentages of ketotifen fumarate dissolved after 1 minute can be arranged in the following order: $F_c9 > F_c13 > F_c1 > Fc2 > F_c11 > F_c3 > F_c12 > F_c16$.

F_C9 containing the complex system (KF: 2-HP-βCD), Ac-di-sol (5%w/w), Avicel PH101(10%w/w) as a binder and mannitol as diluent , showed the highest amount of drug dissolved after 1 minute and minimum buccal disintegration time. Therefore, F_C9 was subjected to bioequivalence studies.

In-vivo Study:

Data from HPLC were presented as ratios of the peak area of the drug (ketotifen fumarate) to the peak area of the internal standard (Metrinidazole) for each sample. Concentrations of the samples withdrawn from volunteers were then determined by comparing the test samples. All the pharmacokinetic parameters were evaluated using WinNonLin® Professional. The mean plasma concentration–time courses for KF following the administration of FDSLTs F9 (contains KF without compelxation with 2HP-βCD); Fc9 and Zaditen® tablet in six healthy volunteers (figure 8). The rate and extent of absorption of KF were found to be different following the three treatments, expressed with higher C_{max} by about 60% and 90% for both FDSLTs of F9 and Fc9 respectively, and earlier t_{max} (by 1 h) values for both of FDSLTs F9 and Fc9 compared with Zaditen®. The mean C_{max} estimated from F9 and Fc9 were 25.578±2.65 ng/mL and 30.901±4.963 ng/mL, respectively, while it was 16.0857±1.628, ng/mL for Zaditen® tablets the differences between the three treatments for C_{max} was statistically significantly different ($p < 0.05$). The mean AUC_{0-24} estimate from FDSLTs was which reflects the total amount of drug absorbed over the 24 h time period, was found to be 161.237 ±16.78 ng h/mL, 210.102±36.99 ng h/mL and 246.192±32.33 ng h/mL for Zaditen® tablets,F9,Fc9 respectively, and determined to be statistically significant different ($p < 0.05$).

Moreover, it was worthy to note that the relative bioavailability for Fc9 of ketotifen fumarate fast disintegrating sublingual tablets was much higher than that of F9. The relative bioavailability of Fc9 was 152.45% compared to 130.304% for F9 when Zaditen® tablets were taken as reference standard.

The higher C_{max} and faster t_{max} observed after FDSLTs F9 and Fc9 than the commercially available conventional tablet (Zaditen®) may be attributed to the rapid disintegration and dissolution of the drug in the saliva even with the absence of water. Moreover in case of FDSLTS, the drug absorbed through the epithelium of sublingual membrane of the buccal mucosa and consequently the bioavailability may increase [19]. Moreover, the rapid and efficient absorption of KF from the buccal mucosa, pharynx and esophagus as the saliva passes down into the stomach (pregastric absorption)[20] resulting in a decreased pre-systemic biotransformation. The increased relative bioavailability of Fc9 compared F9 might be due to the effect of 2-HP-β CD incorporated product which have the ability to interact with macromolecules of sublingual membrane more efficiently causing marked improvement in the drug sublingual absorption [21, 22]. The ability of 2-HP-β CD to augment the extent and stability of supersaturated solutions of various poorly water soluble drug candidates with consequent improvement of their oral bioavailability has been assessed by Vandecruys *et al* [23]. An additional factor that could contribute to the improved of oral absorption and enhanced bioavailability of drugs by hydrophilic cyclodextrins is the increased permeation of drug molecules across the membrane lipid bilayers, as a result of their enhanced availability at the biological barrier and the alteration of the membrane fluidity [24-26].

Conclusion

The development of KF fast disintegrating sublingual tablets containing 2-HP-β CD as a complex with KF is a promising formula resulted in successful KF delivery to blood stream with significantly higher bioavailability when compared to the commercial product. The study suggests that (Fc9) formula developed in this piece of work may be an alternative to conventional formulae of KF, such as oral tablets, that are reported to suffer from extensive hepatic metabolism or that are not convenient to the geriatric or pediatric patients who have swallowing difficulties.

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Table 1: composition of ketotifen fumarate fast disintegrating sublingual tablets using factorial design. All formulae contained KF (1.38mg), magnesium stearate (1%w/w), Aerosil 200 (2%w/w), mint flavor (0.5%w/w) and aspartam (1%w/w).

Formula No	Disintegrant	Binder	Diluent
F1	3% Ac-di-sol	10% Avicel PH-101	Mannitol
F2		10% Avicel PH-101	Lactose
F3		10% PEG 6000	Mannitol
F4		10% PEG 6000	Lactose
F5	3% Explotab	10% Avicel PH-101	Mannitol
F6		10% Avicel PH-101	Lactose
F7		10% PEG 6000	Mannitol
F8		10% PEG 6000	Lactose
F9	5% Ac-di-sol	10% Avicel PH-101	Mannitol
F10		10% Avicel PH-101	Lactose
F11		10% PEG 6000	Mannitol
F12		10% PEG 6000	Lactose
F13	5% Explotab	10% Avicel PH-101	Mannitol
F14		10% Avicel PH-101	Lactose
F15		10% PEG 6000	Mannitol
F16		10% PEG 6000	Lactose

Table 2. Randomization plan of two Ketotifen fumarate formulae F9 and Fc9 FDSLTs. The conventional product Zaditen® (1mg) tablets

Volunteer Number	Phase I	Phase II	Phase III
1	F9	Fc9	Zaditen
2	Fc9	F9	Zaditen
3	Zaditen	F9	Fc9
4	F9	Zaditen	Fc9
5	Fc9	Zaditen	F9
6	Zaditen	Fc9	F9

Table 3. Evaluation data of the prepared KF Fast disintegrating sublingual tablets.

Formula number	Mean Diameter (cm) ± S.D.	Mean Thickness (cm) ± S.D.	% Drug Content ± S.D.	Hardness ±S.D** (Kg)	% Loss in tablet weight (Friability)	Average Disintegration Time ±S.D.* (Seconds)
F1	0.705 (±0.012)	0.209 (±0.012)	105.62 ±0.81	6.8475±0.2085	0.768	64.52±4.435
F2	0.708 (±0.014)	0.205 (±0.007)	93.61±1.472	6.319±0.104	0.829	66.17±3.11
F3	0.714 (±0.002)	0.206 (±0.015)	112.71±2.01	7.175±1.023	0.753	61.15±6.20
F4	0.709 (±0.000)	0.200 (±0.019)	96.25 ±0.932	7.6185±0.846	0.896	77.227±6.38
F5	0.711 (±0.019)	0.215 (±0.008)	109.62±2.57	6.5815±0.632	0.947	72.49±6.59
F6	0.702 (±0.007)	0.216 (±0.022)	101.55±0.98	6.766±0.462	0.663	84.558±4.12
F7	0.727 (±0.003)	0.209 (±0.009)	97.364±1.49	6.825±0.316	0.825	87.95±5.28
F8	0.720 (±0.014)	0.209 (±0.009)	102.55±3.11	7.225±0.881	0.654	100.20±6.615
F9	0.712 (±0.011)	0.213 (±0.019)	94.317±3.81	4.14±0.1565	0.397	24.13±2.012
F10	0.709 (±0.016)	0.211 (±0.016)	112.17 ±0.96	4.49±0.285	1.28	34.79±3.76
F11	0.710 (±0.002)	0.209 (±0.035)	99.037±1.95	5.47±0.185	0.479	37.68 ±1.55
F12	0.708 (±0.089)	0.204 (±0.004)	105.810±2.0	5.395±0.612	0.862	48.08±4.784
F13	0.709 (±0.029)	0.200 (±0.000)	93.91 ±1.70	4.26±0.218	0.975	28.625±2.63
F14	0.715 (±0.202)	0.201 (±0.003)	90.48 ±1.492	4.78±0.571	1.13	35.675±4.405
F15	0.710 (±0.169)	0.216 (±0.013)	109.05±2.31	4.67±0.375	0.812	44.195±3.37
F16	0.700 (±0.092)	0.218 (±0.018)	98.49±1.51	4.85±0.138	0.587	49.525±2.682

Table 4. Characterization of ketotifen fumarate/ 2-HP-β-CD fast disintegrating sublingual tablet

Formula Number	% of drug content ±S.D.	Hardness (Kg)±S.D.	Friability	In-vitro disintegration time(sec.)±S.D	Disintegration Time in the Buccal Cavity (sec.)	% of KF after 1 minute
F_C1	99.18±0.99	6.57±0.74	0.795	57.27±3.57	68.2±4.63	70.24
F_C2	101.58±1.37	6.31±0.42	0.903	1460.42±4.	43.11±3.02	66.34
F_C3	99.91±2.15	7.08±1.34	0.779	53.79±2.12	54.6±5.36	58.36
F_C9	98.18±2.65	4.452±0.72	0.405	421.26±2.7	21.19±2.89	80.26
F_C11	102.47±0.93	4.58±0.84	0.479	36.87±3.15	39.27±4.14	61.71
F_C12	99.33±1.97	5.32±0.31	0.748	39.79 ±6.21	70.48±8.50	78.39
F_C13	98.44±1.76	4.71±0.72	00.85	27.80±2.09	27.25±4.82	39.84
F_C16	102.57±3.80	4.08±0.55	0.611	40.15±4.36	46.37±5.43	70.24

Table 5. pharmacokinetic parameters ±S.D of Ketotifen fumarate following the administration of a single oral dose (1.38 mg) of the market formula (Zaditen® tablets), the selected sublingual tablet formula (F9) and (Fc9).

Pharmacokinetic parameter	Formula		
	(Zaditen® tablets)	**F9**	**Fc9**
Cp_{max} (ng/ml)	16.0857±1.628	25.578±2.65	30.901±4.963
t_{max} (hr)	1.9167±0.204	1.167±0.258	1.083±0.186
$AUC_{(0-24)}$ (ng.hr/ml)	161.237 ±16.78	210.102±36.99	246.192±32.33
$AUC_{(0-\infty)}$ (ng.hr/ml)	264.940±22.475	319.894± 69.137	382.166±55.278
K (hr^{-1})	0.038817 ±0.0094	0.0434 ±0.0038	0.0435 ±0.0055
$t_{½}$ (hr)	18.567±3.615	16.086±1.487	16.234±2.211

* $t_{1/2}$: Elimination half-life. **K: Elimination rate constant.

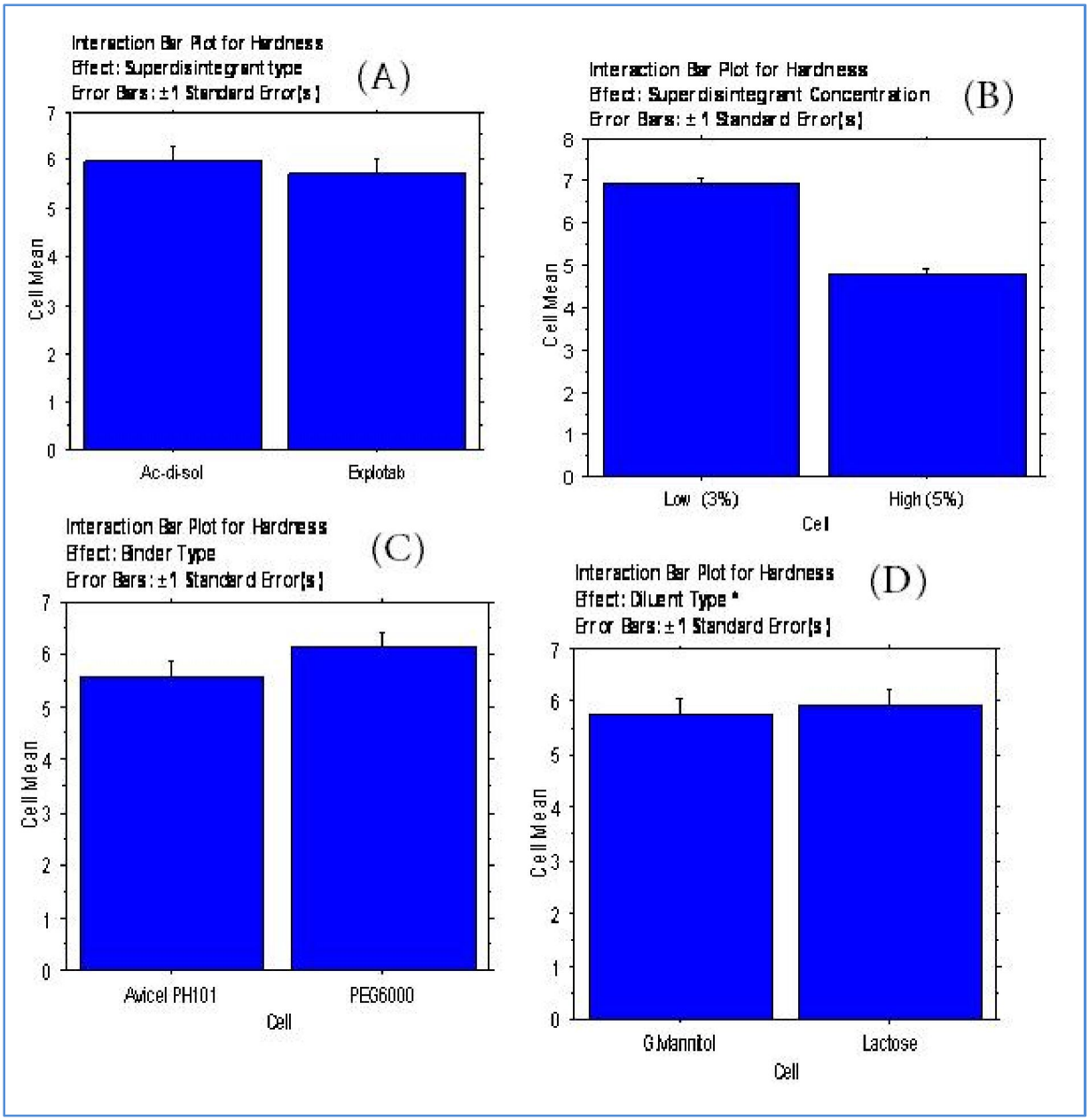

Figure 1. Chart plots for the mean effect of tablets hardness of different formulae from Ketotifen fumarate fast disintegrating sublingual tablets.

(a) Superdisintegrant type (b) Superdisintegrant concentration

(c) Diluent type (d) Binder type

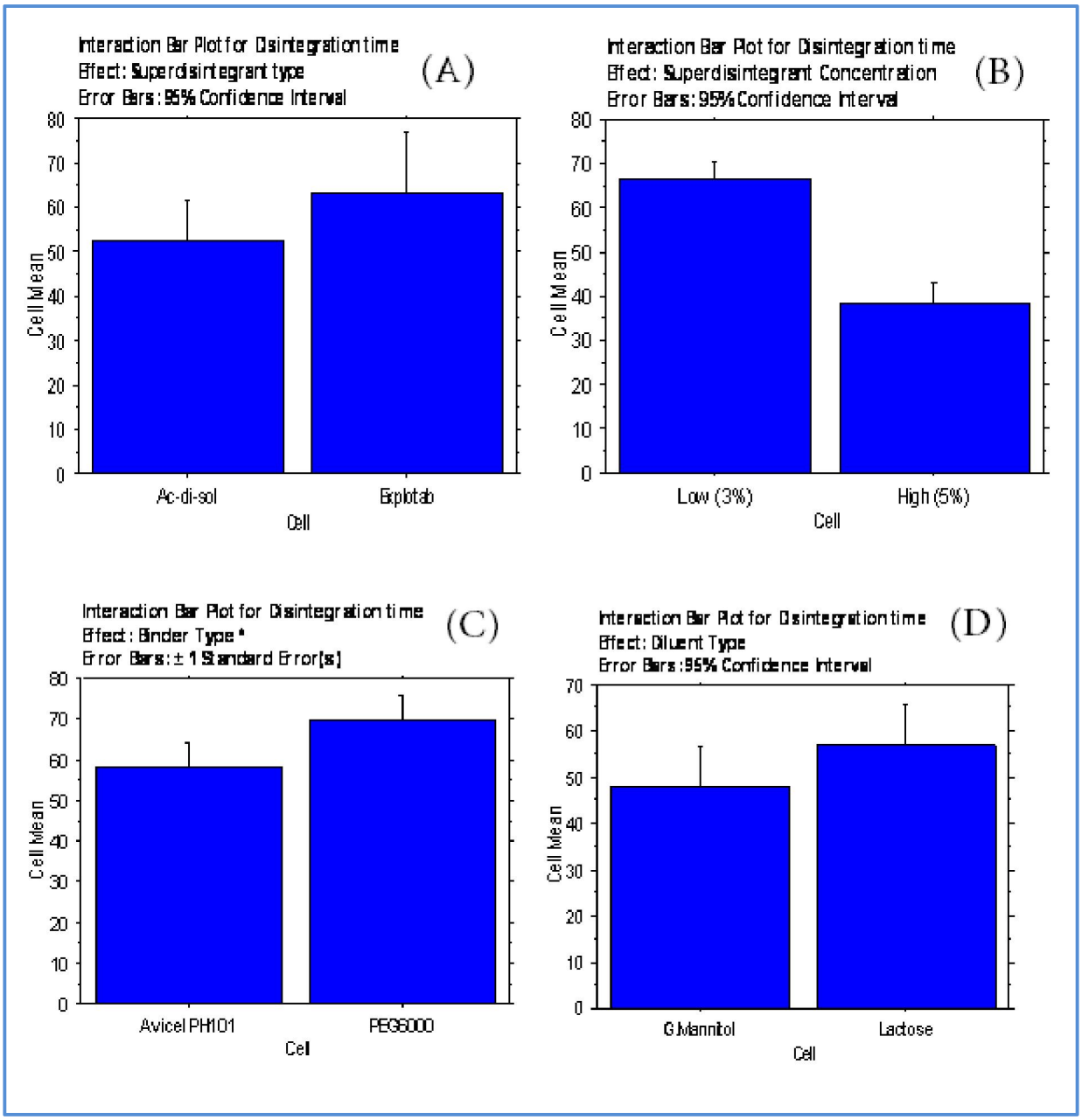

Figure 2: Chart plots for the mean effect of tablets disintegration time of different formulae From Ketotifen fumarate Fast disintegrating sublingual tablets.
(a) Superdisintegrant type (b) Superdisintegrant concentration
(c) Binder type (d) Diluent type

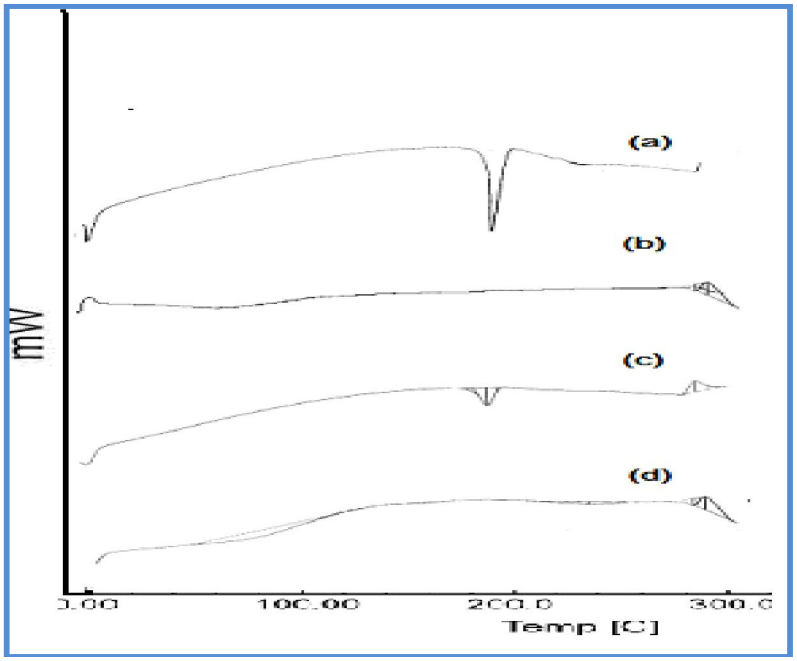

Figure (3): DSC thermograms of KF/2-Hydroxyypropyl-β-cyclodextrin solid systems. (a) Pure Ketotifen fumarate; (b) Pure HP-β-CD (c) Physical mixture (d) Coprecipitation.

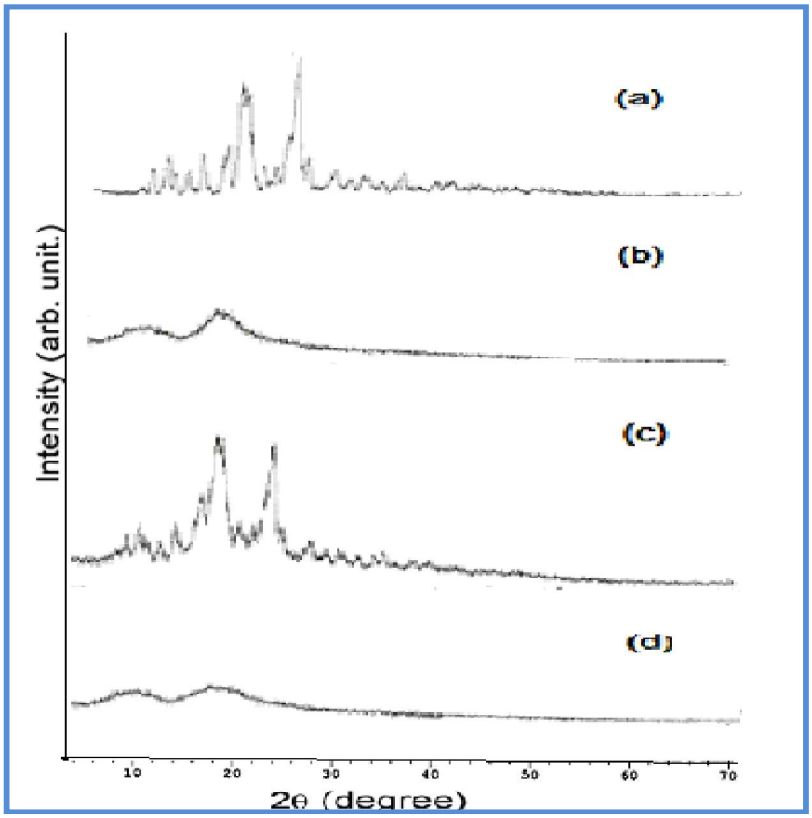

Figure (4): X-ray diffraction patterns of KF/2-Hydroxypropyl-β-cyclodextrin solid systems. (a) Pure Ketotifen fumarate (b) Pure HP-β-CD(c) Physical mixture (d) Coprecipitation

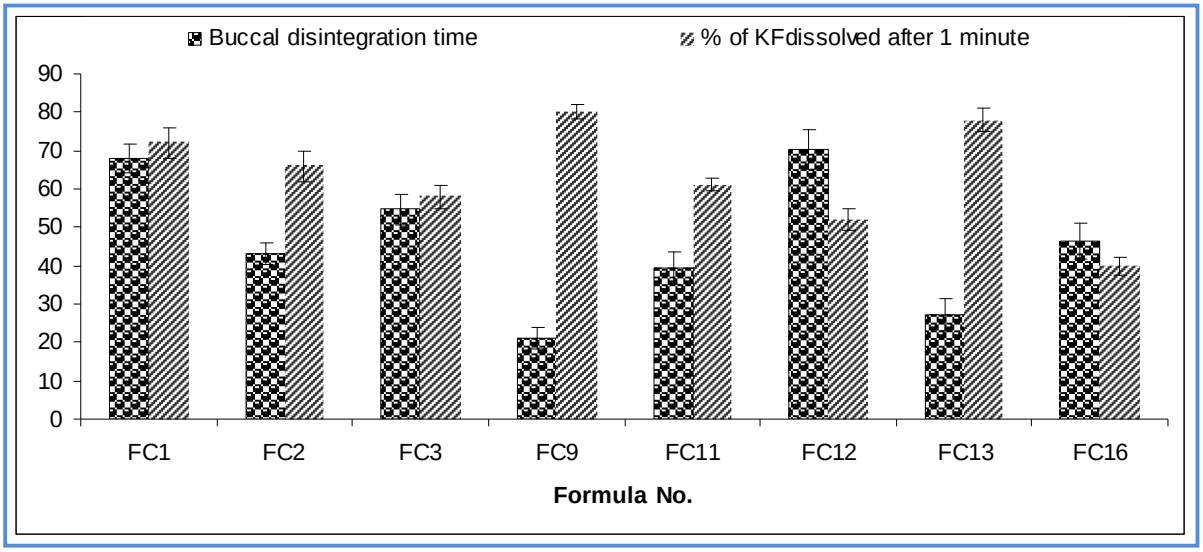

Figure 5: The average buccal disintegration time and the percent of KF after1 minute of the selected KF fast disintegrating sublingual tablets

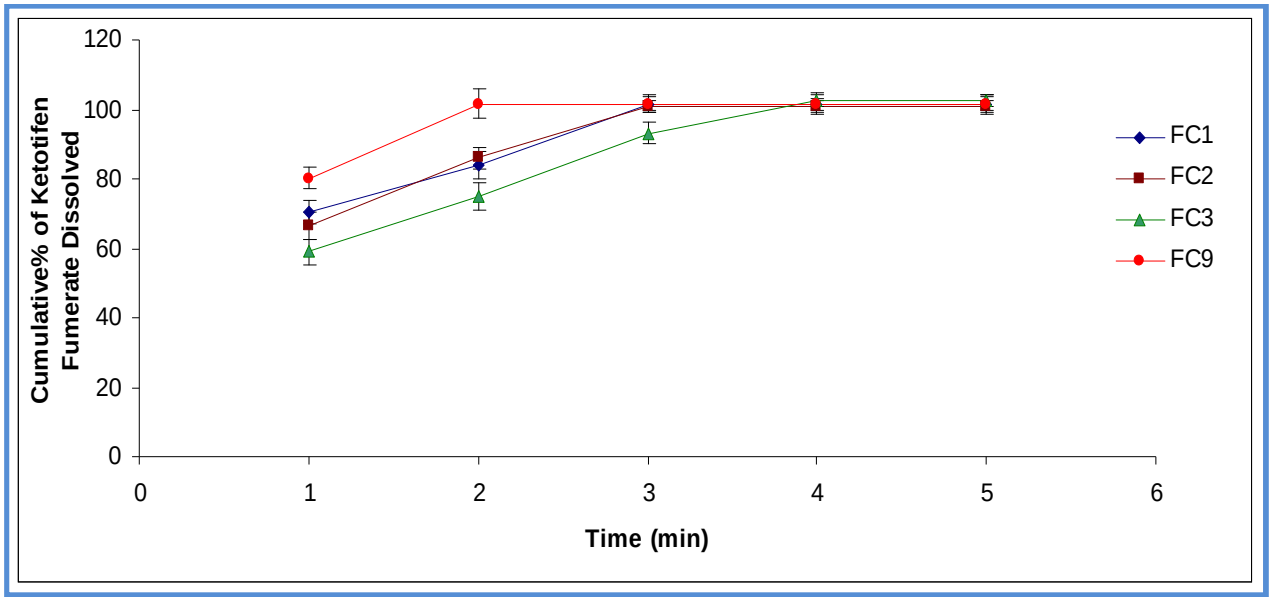

Figure 6: Dissolution of ketotifen fumarate from the selected tablet formulae for choosing the best formula (n=3± S.D.).

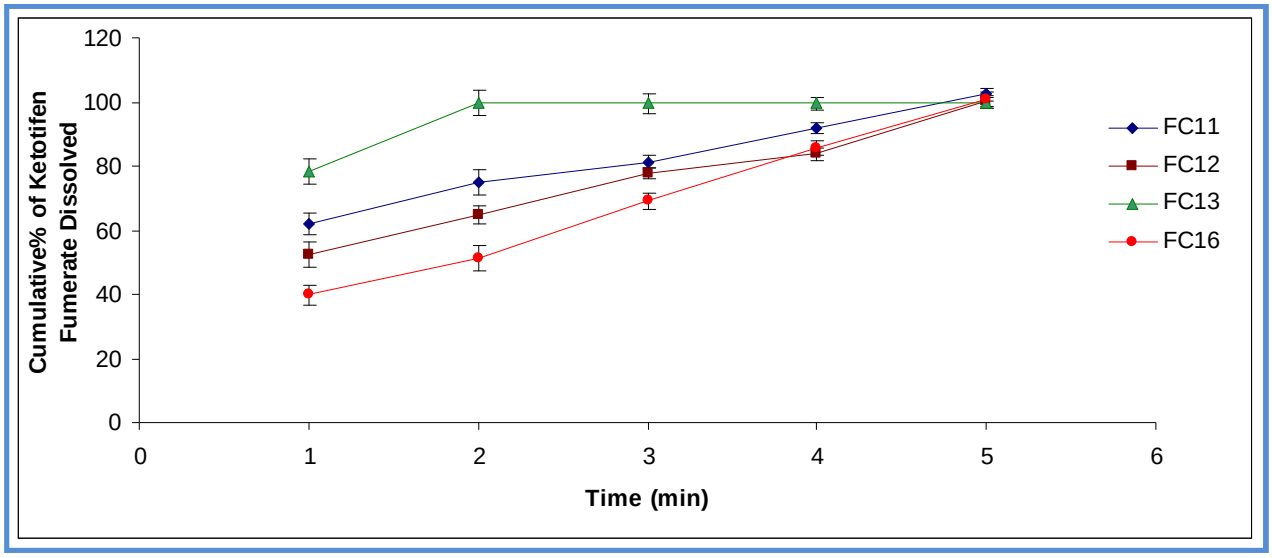

Figure 7: Dissolution of Ketotifen Fumarate from the selected Tablet Formulae for choosing the best formula (n=3± S.D.)

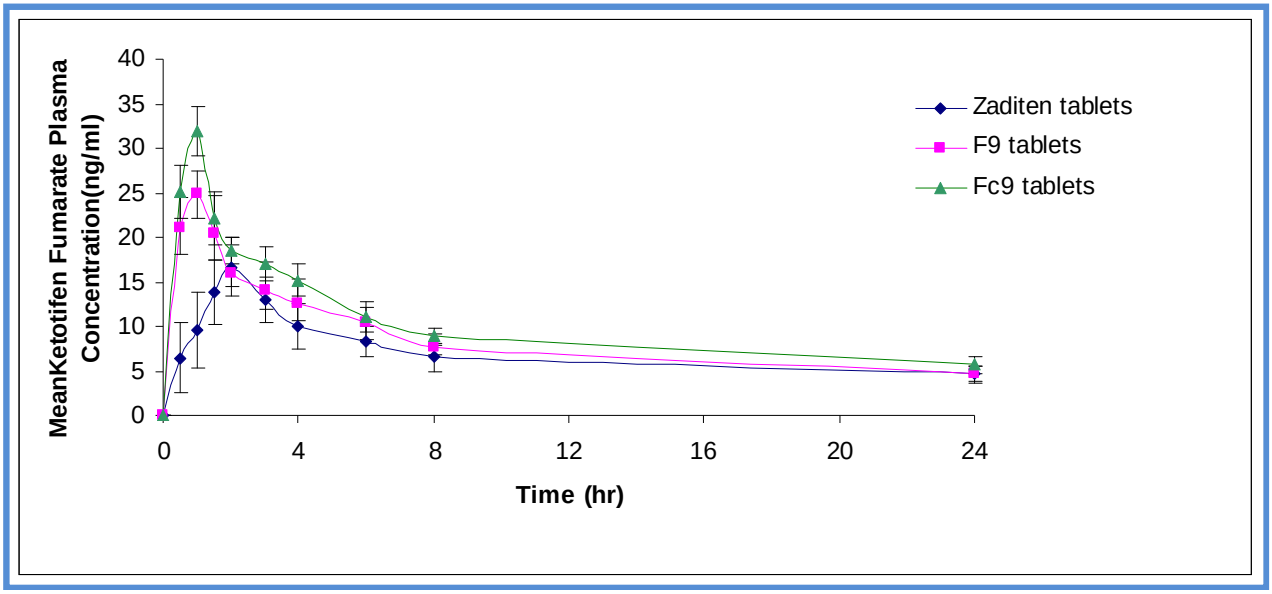

Figure 8: Plasma concentration of ketotifen fumarate following the administration of treatments Zaditen® tablets, F9 tablets and Fc9 tablets. Data represent the mean values of n=6 ± S.D.