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Research Article

FORMULATION AND INVITROEVALUATION OF FAST DISSOLVING TABLETS OF FLECAINIDE ACETATE

SOUMYA.M*, Y.A.CHOWDARY, A.MADHURI, M.D.SINDHUSHA, T.NAGARANI, B.ARUNA, MANASA.V

Department of Pharmaceutics,NRI College Of Pharmacy, Pothavarappadu, Agiripalli Mandal, Vijayawada- 521212, (A.P), India.
Email: soumyamissula@gmail.com

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ABSTRACT

Flecainide acetate is a class Ic anti arrhythmic agent used to prevent and treat tachyarrhythmias, a wide variety of cardiac arrhythmias including paroxysmal atrial fibrillation,paroxysmal supraventricular tachycardia and ventricular tachycardia.In the current study an effort was made to prepare the fast dissolving tablets of flecainide acetate by direct compression method so as to increase its dissolution rate in the oral cavity.Flecainide acetate fast dissolving tablets were fabricated using Crospovidone sodium (CPS),Croscarmellose sodium (CCS) in different concentrations at ratios of 10:90,20:80,25:75,50:50,75:25,80:20 and 90:10 and seven batches (F1-F7)were prepared.The prepared blend was analysed for several precompressional parameters like angle of repose, bulk density,tapped density,hausners ratio and Carr's compressibility index. The tablets were evaluated for shape and color, thickness, hardness, weight variation, content uniformity,friability,disintegration time,wetting time and invitro dissolution studies.Formulation F3 showed complete disintegration in 15secs.Invitro dissolution of formulation F3 with superdisintegrants Crospovidone and Croscarmellose at ratios of 25:75 showed first order kinetics with Higuchi mechanism showed 100 % release at the end of eight minutes. The drug release was faster in F3 and completed at the end of 8 minutes but the marketed TAMBOCOR-100mg showed complete release at the end of 45 minutes.Optimized formulation F-3 was subjected to stability studies for three months at 45 ºC with 75±5% RH as per ICH guidelines and no significant changes were reported.

Keywords: Flecainide acetate, Crospovidone sodium, Croscarmellose sodium, Fast dissolving tablets.

INTRODUCTION

The concept of FDTs came into view with an objective of increased patient compliance[1]. The Center for Drug Evaluation and Research (CDER), US FDA defined fast dissolving tablets (FDT) as "A solid dosage form containing medicinal substances, which disintegrate or dissolve rapidly, usually within a matter of seconds, when placed upon the tongue".[2]FDTs disintegrate and/or dissolve instantaneously in the saliva without the use of water. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets[3,4,5].The basic approach in development of MDT is the use of superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), crosslinked polyvinylpyrollidone (Crospovidone) etc., provide instantaneous disintegration of tablet after putting on tongue, there by release the drug in saliva[6,7].

Flecainide acetate is a class Ic anti arrhythmic agent.Chemically it is N-(2-piperidylmethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzamide. Its used to prevent and treat tachyarrhythmias, a wide variety of cardiac arrhythmias including paroxysmal atrial fibrillation,paroxysmal supraventricular tachycardia and ventricular tachycardia[8].For the treatment of supraventricular tachychardias and paroxysmal atrial flutter,a starting dose of 50mg twice a day was used.For the treatment of life-threatening ventricular arrhythmias,a starting dose of 100mg twice a day was used. Flecainide is almost completely absorbed after oral administration and does not undergo extensive first-pass metabolism. The bioavailability from flecainide acetate tablets has been reported to be about 90%. It is excreted mainly in the urine, approximately 30% as unchanged drug and the remainder as metabolites[9]. About 5% is excreted in the faeces. Excretion of flecainide is decreased in renal failure, liver diseases, heart failure, and in alkaline urine. Haemodialysis removes only about 1% of unchanged flecainide.The present work dealt with the preparation of fast dissolving tablets of flecainide acetate using different concentration ratios of crospovidone and croscaramellose sodium.Microcrystalline cellulose was used as the diluent,sodium saccharin was used as a sweetener,magnesium stearate and talc were used as glidant and lubricant respectively in all the batches F1-F7.

MATERIALS AND METHODS

Flecainide acetate was a gift sample obtained from Orchid Chemicals & Pharmaceuticals,Chennai. Crospovidone and croscarmellose, microcrystalline cellulose were purchased from Signet Chemicals, Mumbai. Sodium saccharin, talc and magnesium stearate were purchased from National Scientifics, Vijayawada. All reagents used were of analytical grade.

Experimental Methodology

Preformulation studies

Drug-Excipient Compatibility study[10,11]

The study was determined to carry out the compatibility of drug with different excipients.Compatibility of the drug with various excipients was studied using Fourier Transform Infra Red Spectroscopy(FTIR) to detect any changes in the chemical constitution of the drug after their combination.

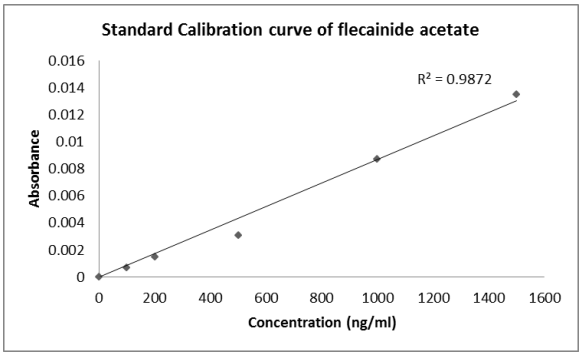

Fig. 1: Standard Calibration curve of flecainide acetate

Preparation of Standard Calibration Curve of Flecainide acetate

An accurately weighed 100mg of pure flecainide acetate was transferred to a clean, dry, calibrated 100ml volumetric flask, dissolved in 5ml of 0.075 N HCl[12] and made up to the volume with the same.1ml of prepared solution was transferred to a clean, dry, calibrated 100ml volumetric flask and the volume were made up with 0.075 N HCl.Solutions ranging in concentrations of 100ng/ml to 1500 ng/ml were made from the stock solution.The absorbance of the solution was measured at 296nm, using 0.075 N HCl as blank. A graph of Concentration Vs absorbance was plotted which indicated in compliance to Beer's law in the concentration range[13].

Standard plot of flecainide acetate

Standard plot of flecainide acetate was plotted by taking concentration(ng/ml) on X-axis and absorbance on Y-axis, the plotted graph is shown in fig.1.

Physical characterization of the blend

The prepared blend was analysed for angle of repose, bulk density, tapped density, compressibility index and hausner's ratio.

Determination of Angle of repose

The flow property was determined by measuring the Angle of Repose. It is the maximum angle that can be obtained between the freestanding surface of a powder heap and the horizontal plane. Values of θ are rarely less than 20°, and values of up to 40° indicate reasonable flow potential. Above 50°, however, the powder flows only with difficulty if at all. Certain amount of the sample was taken in a funnel fixed in a holder, 2.5cm above the surface at an appropriate height and a graph of sheet was placed below the funnel. The sample was passed through the funnel slowly. The height of the powder heap formed was measured. The circumference of the heap formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined using the below formula

$$\theta = \text{Tan}^{-1} (h/r)$$

Where, h = height the pile;r = radius of the pile;θ = Angle of repose.

Determination of Bulk density tapped density,compressibility index and hausners ratio

A fixed quantity of the powder (W) was introduced into a 100 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formulas:

Bulk density = W / V_0 Tapped density = W / V_f

Where, W = weight of the powder; V0 = initial volume.; Vf = final volume.

Compressibility index (Carr's index)

Compressibility index is an important measure that can be obtained from the bulk and tapped densities.

Compressibility index, $(C_I) = 100 (V_0 - V_f) / V_0$

Hausner's Ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density/Bulk density

Formulation of Tablets Using Direct Compression Method

Weigh all the ingredients accurately and pass through sieve # 36.Mix all the ingredients geometrically except talc and magnesium stearate. Then lubricate the blend with talc and magnesium stearate. Tablets were compressed using 9mm flat face circular punches which were fixed to the 16 station single rotary tablet compression machine (Cadmach, Ahmedabad, India). Table 1 illustrates the formulation design of tablet.

Evaluation of Tablets [14,15,16]

Weight Variation test

Twenty tablets were selected from each formulation and the average weight was determined. The individual tablet weight was compared with the average weight.

Friability

The friability of the tablets was evaluated using a Roche friabilator. It subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm for about 4minutes or 100 revolutions. Pre weighed sample(W_i) of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed(W_f). The friability (F) is given by the formula.

$$F = \frac{W_i - W_f \times 100}{W_f}$$

Table 1: Formulation design of fast dissolving tablets of Flecainide Acetate

S. No.	Ingredients	F1(mg) 10:90	F2(mg) 20:80	F3(mg) 25:75	F4(mg) 50:50	F5(mg) 75:25	F6(mg) 80:20	F7(mg) 90:10
1	Flecainide acetate	100	100	100	100	100	100	100
2	Crospovidone	1.875	3.75	4.69	9.375	14.06	15.0	16.875
3	Croscarmellose Sodium	16.875	15.0	14.06	9.375	4.69	3.75	1.875
4	Microcrystalline Cellulose(PH 102)	122.5	122.5	122.5	122.5	122.5	122.5	122.5
5	Sodium Saccharin	1.25	1.25	1.25	1.25	1.25	1.25	1.25
6	Magnesium stearate	3.75	3.75	3.75	3.75	3.75	3.75	3.75
7	Talc	3.75	3.75	3.75	3.75	3.75	3.75	3.75
Total (mg)		250	250	250	250	250	250	250

Ratio of Crospovidone: Croscarmellose sodium

Hardness

The hardness of the prepared tablets was estimated using Monsanto hardness tester[17]. Three tablets from each formulation batch were selected and force is applied diametrically. It is expressed in kg/cm^2.

Thickness

The tablet thickness was calculated using Vernier calipers. It is expressed as mm.

In vitro Disintegration test

The in vitro disintegration was performed in USP disintegration apparatus. The operation was done by placing six tablets in each tube and the time required for the complete disintegration with no palpable mass was noted in seconds[18].

Wetting Time

A piece of tissue paper folded twice was placed in a petri dish (i.d =6.5cm) containing 10ml of water, a tablet was put on the paper and the time for complete wetting was noted. Three trials from each batch were performed.

In vitro Dissolution Study

In vitro dissolution was performed using USP dissolution apparatus type II (paddle) with a dissolution medium of 900ml of 0.075N HCl at 50 rpm[12] and temperature was maintained at 37±0.5°C. 5 ml aliquots were withdrawn at the specified time intervals and replaced with equal amount of the buffer to maintain sink conditions. The samples withdrawn were analysed spectrophotometrically at 296nm using a UV-Visible Spectrophotometer.

Stability studies [19,20]

The optimised formulation was evaluated for the stability studies at temperature and relative humidity of 45ºC/75% RH for a period of one month and evaluated for various parameters during the stress conditions.

RESULTS AND DISCUSSION

Drug-Excipient Compatibility Studies

The FT- IR Spectrum of pure flecainide acetate was compared with the FT- IR spectrum of physical mixture of drug with microcrystalline cellulose, crospovidone and croscarmellose sodium.(fig.no.2-5)The characteristic peaks of pure drug and physical mixtures occur in the following wavenumber region (cm^{-1}).

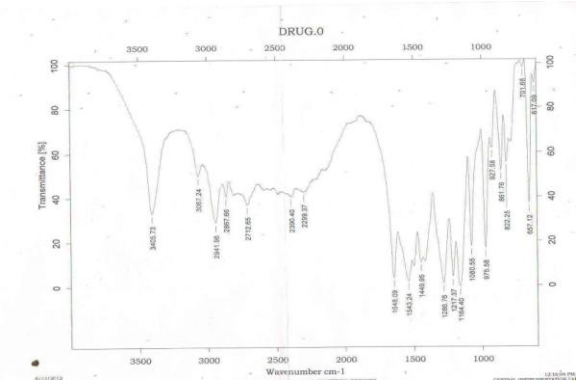

Fig. 2: FTIR spectra of pure flecainide acetate

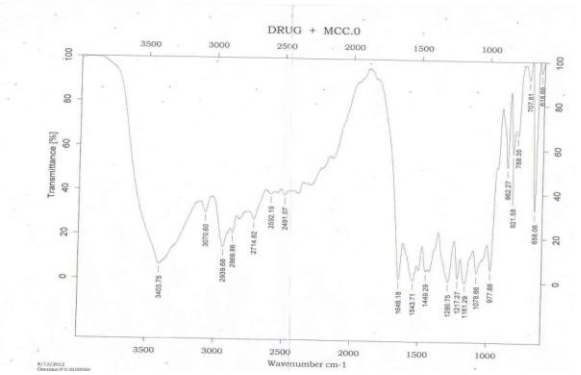

Fig. 3: FTIR spectra of flecainide acetate and MCC

There was no appearance or disappearance of any characteristic peaks. This shows that there is no chemical interaction between the drug and the polymers used.The presence of peaks at the expected range confirmed that the materials taken for the study are genuine and no possible interactions occurred.

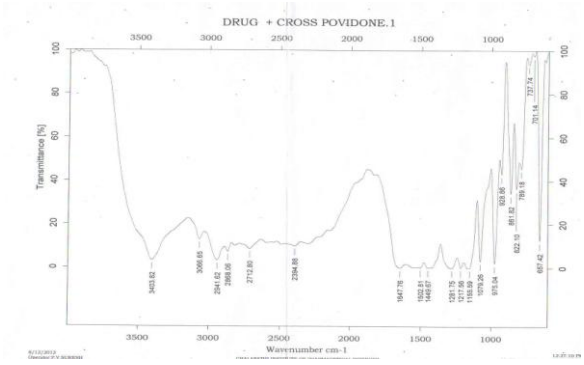

Fig. 4: FTIR spectra of flecainide acetate and Crospovidone

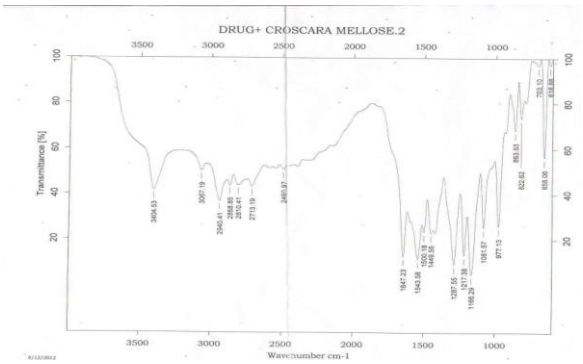

Fig. 5: FTIR spectra of flecainide acetate and Croscarmellose

Evaluation of physical blend:

The physical blend was evaluated for angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. The results were tabulated in table no.2.

Evaluation of fast dissolving flecainide tablets:

The fast dissolving flecainide tablets were evaluated for post compressional parameters like weight variation, friability, hardness, thickness, in vitro disintegration and wetting time. The results were tabulated in table no.3.

Table 2: Results of pre-compression parameters:

Formulation Code	Angle of Repose(º) Mean±S.D	Bulk density(gm/cc) Mean±S.D	Tapped density(gm/cc) Mean±S.D	Compressibility index (%) Mean±S.D	Hausner's ratio Mean±S.D
F1	27.18±0.32	0.4158±0.0009	0.4830±0.0012	13.92±0.39	1.1618±0.0052
F2	28.57±0.20	0.4276±0.0014	0.4807±0.0012	11.04±0.50	1.1242±0.0063
F3	29.42±0.13	0.4045±0.0012	0.4691±0.0006	13.75±0.36	1.1595±0.0049
F4	28.37±0.37	0.4035±0.0021	0.4720±0.0017	14.52±0.48	1.1699±0.0065
F5	28.29±0.58	0.4270±0.0014	0.4676±0.0017	8.682±0.59	1.0951±0.0065
F6	29.19±0.33	0.3973±0.0016	0.4633±0.0016	14.23±0.59	1.1660±0.0070
F7	28.21±0.04	0.4106±0.0008	0.4858±0.0018	15.46±0.30	1.1830±0.0042

All values were expressed as Mean±S.D,n=3

Table 3: Results of post-compression parameters:

Formulation Code	Weight variation(mg) Mean±S.D	Friability (%) Mean±SD	Hardness (Kg/cm^2) Mean±S.D	Thickness (mm) Mean±S.D	Invitro disintegration time(secs) Mean±S.D	Drug content uniformity (%) Mean±S.D	Wetting time (secs) Mean±S.D
F1	255±0.05	0.54±0.03	3.5±0.87	3.0±0.09	20±0.57	99.29±0.05	30±0.52
F2	252±0.15	0.64±0.05	4.0±0.54	3.2±0.15	15±0.57	99.46±0.1	31±0.15
F3	248±0.12	0.59±0.13	4.2±0.59	3.5±0.15	15±0.482	99.66±0.04	31±0.52
F4	250±0.06	0.56±0.1	3.4±0.66	3.1±0.25	20±1.15	99.23±0.02	35±1.69
F5	253±0.09	0.79±0.06	3.5±0.98	3.5±0.8	25±1.93	99.49±0.05	30±0.56
F6	245±0.15	0.54±0.19	3.5±0.14	3.3±0.35	25±0.05	99.72±0.04	35±1.02
F7	249±0.19	0.77±0.05	3.9±0.19	3.4±0.65	30±0.98	99.76±0.04	40±1.21

All values were expressed as Mean±S.D, n=3

Fig. 6: Fast dissolving flecainide acetate tablet subjected for Wetting time Evaluation

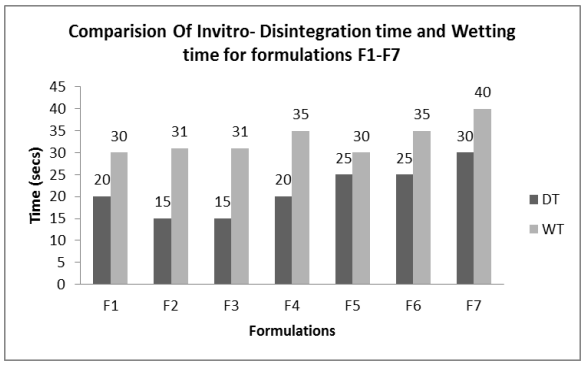

Fig. 7: Comparision Of Invitro- Disintegration time and Wetting time for formulations F1-F7

The fast dissolving flecainide acetate tablets were designed using two super disintegrants Crospovidone and croscarmellose. A total of seven formulations (F1-F7)were prepared at ratios 10:90,20:80,25:75,50:50,75:25,80:20,90:10 of crospovidone and croscarmellose sodium respectively.The quality control tests adopted were depicted in tables 3 and 4.There was no significant weight variation observed within average weight and individual weight. The % friability of the tablets was well within the acceptable range. The percentage friability ranged from 0.54±0.03% to 0.79±0.06%.The hardness of tablets ranged between 3.4±0.66 and 4.2±0.59 Kg/cm^2.The thickness of the tablets ranged from 3.0±0.09 to 3.5±0.15 mm. The tablets showed very fast disintegration time, lesser concentrations of crospovidone and higher concentrations of croscarmellose resulted in complete disintegration within 15 secs. The invitro disintegration time for the prepared fast dissolving tablets ranged between 15±0.57 and 30±0.98 secs. The drug content within all formulations in within the range of 99.23±0.02 and 99.76±0.04%.Wetting time corresponds to the time taken for the tablet for the tablet to disintegrate when kept motionless on the tongue. The wetting time was in range of 30±0.52 and 40±1.21secs.

Invitro Dissolution studies

All the seven formulations were subjected to in-vitro dissolution studies by using 0.075N HCl as dissolution medium. In-Vitro release studies of all formulations were plotted and shown in the fig.no.8.Formulations F1,F2 exhibited higher concentrations of croscarmellose showed cumulative drug release of 59.29% and 85.84% respectively at the end of ten minutes. Formulation F3 showed 100% cumulative drug release at the end of eight minutes. Formulations F4,F5,F6,F7 showed 90.58%,52.35%,22.46%,61.84% respectively at the end of ten minutes. Out of all seven,F3 showed 100% release within eight minutes and it is compared with the marketed formulation(TAMBOCOR 100mg)which showed 100%release at the end of 45 minutes.The drug release followed first order kinetics for all formulation batches.(F1-F7) on the basis of regression value(R value is greater for first order).To ascertain the mechanism of drug release the data was subjected to Higuchi & korsmeyer Peppas equations. Formulations F1- F7 showed Higuchi mechanism of drug release.The optimised F3 formulation with superdisintegrants Crospovidone and Croscarmellose at ratios of 25:75 showed first order kinetics with Higuchi mechanism of drug release. Medium concentrations of crospovidone exhibits ideal results at very low concentration ratios it is not sufficient for better drug release within short time.

Comparision with marketed formulation TAMBOCOR-100mg

The optimized formulation F3 was compared with marketed tablet (TAMBOCOR 100mg) for different tests like hardness, friability, thickness, uniformity of drug content, in-vitro disintegration time, wetting time and in-vitro dissolution study.The results are tabulated in table no.5

Table 4: Kinetic values obtained from Invitro-release data for formulations F1-F7.

Formulation code	Zero order R value	First order R value	Higuchi R value	korsmeyer Peppas R value	'n'value (release exponent)
F1	0.9511	0.9811	0.9951	0.9850	0.4758
F2	0.8678	0.9627	0.9834	0.9803	0.2741
F3	0.8911	0.9980	0.9833	0.9708	0.3377
F4	0.8803	0.9747	0.9797	0.9738	0.3402
F5	0.9409	0.9671	0.9911	0.9683	0.5444
F6	0.9669	0.9712	0.9845	0.9769	0.6514
F7	0.8548	0.9133	0.9986	0.9931	0.5471

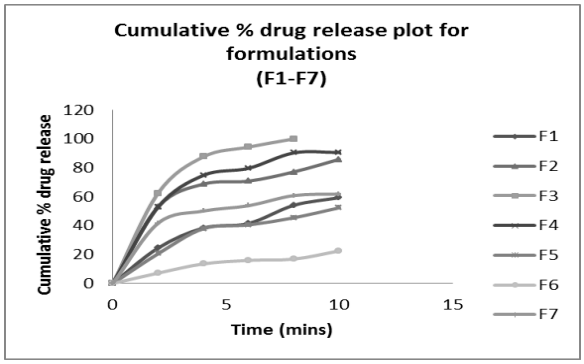

Fig. 8: Cumulative % drug release plot for FDT of Flecainide acetate.

Table 5: Comparision of post-compressional parameters of F3 formulation with Tambocor

Formulation Code	Weight variation(mg) Mean±S.D	Friability (%) Mean±SD	Hardness (Kg/cm²) Mean±S.D	Thickness (mm) Mean±S.D	Invitro disintegration time(secs) Mean±S.D	Drug content uniformity (%) Mean±S.D	Wetting time (secs) Mean±S.D
F3	248±0.12	0.59±0.13	4.2±0.59	3.5±0.15	15±0.482	99.66±0.04	31±0.52
Tambocor 100mg	220±1.56	0.42±1.2	6.5±0.5	3.0±0.6	220±0.5	99.88±1.5	475±1.3

All values were expressed as Mean±S.D, n=3

The results concluded that the marketed formulation showed large difference in the invitro disintegration time and wetting time as compared to F3.F3 showed faster disintegration and wetting time than Tambocor because of the presence of superdisintegrants Crospovidone and Croscarmellose at ratios of 25:75.

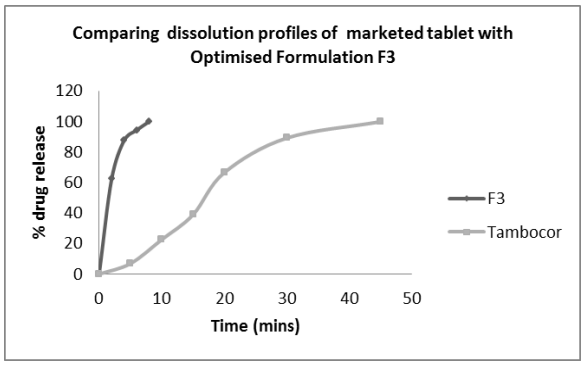

Fig. 9: Comparision of dissolution profile of F3 with Tambocor

The dissolution profile suggested that the drug release was faster in F3 and was completed at the end of 8 minutes but the marketed formulation showed complete release at the end of 45 minutes.

Table 6: Stability studies for three months at 45 ºC with 75±5% RH

Parameters	Initial	At the end of 1st month	At the end of 2nd month	At the end of 3rd month
Hardness((Kg/cm²)	4.2±0.59	4.0±0.12	4.2±2.5	4.0±1.59
Inviter-disintegration time(sacs)	15±0.482	16±0.56	15±0.19	18±1.15
Drug content(%)	99.66±0.04	99.5±1.56	99.2±1.02	98.92±0.33
Cumulative% of drug release	100.1	99.91	99.45	99.56

Both the formulations showed no significant variations in all the parameters and were stable for a period of three months.

Stability Studies

Optimized formulation F-3 was subjected to stability studies for three months at 45 ºC with 75±5% RH as per ICH guidelines. The tablets were analyzed for Hardness, In-Vitro disintegration time, drug content and cumulative % drug released till a period of 3 months. The results were shown in table no.6.

CONCLUSION

The fast dissolving tablets of flecainide acetate proved to show better release profile in all aspects as compared to marketed formulation.The use of superdisintegrants crospovidone and croscarmellose showed faster disintegration and dissolution profile. Ideally F3 formulation was considered as optimized which showed 100% drug release at the end of 8 minutes.All the formulations followed first order kinetics with higuchi mechanism of drug release.(F2-F7)

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