Research Article

Formulation and Development of Fast Disintegrating Efonidipine Tablets: Functionality of Superdisintegrants

S.K.Sathish[1*], V.P. Pandey[2]

[1] Department of Pharmaceutics, Ultra College of Pharmacy, Madurai, Tamilnadu, India.

[2]Department of Pharmacy, Annamalai university, Annamalai nagar, Chidambaram, Tamilnadu, India.

***Corresponding author's E-mail:** krrs78@gmail.com

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ABSTRACT

Efnodipine, a calcium channel blocker, is used for hypertension and angina pectoris. Efnodipine fast-disintegrating tablets (FDT) have been prepared by kneading method. In the present study cyclodextrins (βCD and HPβCD) and surfactants (Kolliphor HS15) were tried to enhance the solubility and dissolution rate of Efnodipine. The individual main effects and combined (interaction) effects of cyclodextrins and surfactants on the solubility and dissolution rate of Efnodipine was evaluated in a series of 2^2 factorial experiments.) The hardness, friability, drug content and disintegration time, *in vitro* release and stability parameter has been studied. Hardness of the tablets was in the range 6.0 –7.5 kg/sq.cm. Percent weight loss in the friability test was less than 0.85% with all the formulations. The disintegration time was in the range 1 –3.5 min. with all the tablets prepared. Drug content of the tablets was within100 ± 2% of the labeled claim. The dissolution efficiency was also increased from 4.56% for formulation E1 to 41.54 % and 36.59 % respectively for formulations E4 and E8. The formulation did not show any change in disintegration time and drug content after stability period. It was concluded that fast disintegrating Efnodipine tablets can be prepared by kneading method using super disintegrants.

Keywords: Efnodipine tablets, cyclodextrins, surfactants (Kolliphor HS15).

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INTRODUCTION

Efonidipine hydrochloride is a di hydro pyridine derivative, that is chemically described as 2-(*N*-benzylanilino) ethyl 5-(5,5-dimethyl-2-oxo-1,3,2λ^5-dioxaphosphinan-2-yl)-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate. The absorption ratio of radioactivity estimated from the sum of biliary and urinary excretions was found to be approximately 62%[1] . The radioactivity was high in the gastrointestinal tract and liver, followed by the adrenal glands, suggesting high rates of metabolism in these regions. The unchanged drug in the plasma accounted for 47.7% of radioactivity at 2hr after ingestion, demonstrating a lower first-pass effect in comparison with other drugs in the same class[2]. In plasma, major metabolites of NZ-105 were: N-de benzylated compound (DBZ), N-dephenylated compound (DPH), oxidative de aminated compound (AL), AL-corresponding pyridine compound (ALP), unknown metabolite M-1 and M-25. NZ-105 was metabolized by N-debenzylation, N-de phenylation, oxidative de amination, ester hydrolysis and oxidation of 1, 4-dihydropyridine ring to its corresponding pyridine[3,4] .

The fast-disintegrating drug delivery systems is rapidly gaining acceptance as an important novel drug delivery system. This delivery system offers better patient compliance than conventional tablet dosage form[5]. Bioavailability of drug from this delivery system is significantly greater than conventional tablets[6]. Fast disintegrating tablets are not only indicated for people having difficulty in swallowing but also ideal for un favorable conditions of administration where water is not available. Syrups are best for pediatrics but they are bulky and drugs are not as stable in liquid form as in solid form[7].After keeping the FDT on tongue, immediately it disintegrates, releasing the drug which dissolves or disperses in the saliva. Some drugs are absorbed from the mouth, pharynx and esophagus, as the saliva passes down into the stomach, in such cases bioavailability of drug is significantly greater than conventional dosage form[8].Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets[9-10]. The effect of functionality difference of the super disintegrants on tablet disintegration has been studied[11].The objective of the present investigation was to develop fast disintegrating The major objective is to enhance the solubility, dissolution rate and bioavailability Efonidipine tablets to evaluate the individual main effects and combined (interaction) effects of cyclodextrins (βCD and HPβCD) and surfactants (Kolliphor HS15and Pluronic F127) a series of 2^2 factorial experiments and to evaluate the feasibility of formulating Efonidipine tablets with enhanced dissolution rate and dissolution efficiency employing drug-CD-surfactant complex systems.

MATERIALS AND METHODS

Efnodipine was gifted sample from M/s Amoli Organics Pvt., Ltd., Mumbai. β-cyclodextrin and hydroxy propyl β-cyclodextrin were gift samples from Signet Chemical Corporation Pvt., Ltd., Mumbai. Pluronic F127(BDH), Kolliphor HS15(SD Fine Chem.).All other materials used were of Pharmacopoeial grade.

Methods

Formulation of Tablets

Employing Drug-CD-Kolliphor HS15Complexesas per a 2^2–Factorial Study: Tablet of Efnodipine (40mg) were formulated employing selected combinations of CD (βCD and HPβCD) and Kolliphor HS15in each case as per a 2^2–Factorial design. For this purpose, 2 levels of CD (0 and 1:2 ratios of drug : CD) and two levels of Kolliphor HS15(0 and 5%) were selected and the corresponding four treatments involved in the 2^2–Factorial study.

Efnodipine Tablets with βCD and Kolliphor HS15

Statistical code as per 2^2–Factorial Design	Description	Formulation code
1	Tablets of efnodipine alone	E1
a	Tablets of efnodipine -βCD (1 : 2)inclusion complex	E2
b	Tablets of efnodipine -Kolliphor HS15(5%) blend	E3
ab	Tablets of efnodipine -βCD-Kolliphor HS15(1 : 2 : 0.05) ternary complexes	E4

Efnodipine Tablets with HPβCD and Kolliphor HS15

Statistical code as per 2^2–Factorial Design	Description	Formulation code
1	Tablets of efnodipine alone	E5 Same as E1
a	Tablets of efnodipine -HβCD (1 : 2)inclusion complex	E6
b	Tablets of efnodipine -Kolliphor HS15(5%) blend	E7 Same as E3
ab	Tablets of efnodipine -HβCD- Kolliphor HS15(1 : 2 : 0.05) ternary complexes	E8

Preparation of Tablets

Tablet of Efnodipine (40mg) were prepared by wet granulation method as per the formulae given in Tables 1-2.

Method

Drug-CD-Kolliphor HS15ternary complex systems as per the formulae given in Tables 1 –2 were initially prepared in each case by kneading method. To the dried ternary complex in the mortar lactose and PVP were added and mixed thoroughly. Water-alcohol (1:1) solution was added and mixed thoroughly to form a dough mass. The mass was passed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60°C for 4 hr. The dried granules were passed through mesh No. 16 to break the aggregates. Cross carmellose sodium, talc and magnesium stearate were passed through mesh No. 100 onto dry granules and blended in a polyethylene bag. The tablet granules were then compressed into tablets on a rotary multi-station tablet punching machine (M/s. Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 6-7 kg/sq.cm using 9 mm round and flat punches.

Evaluation of Tablets

All the tablets prepared are evaluated for i) Content of active ingredient ii) Hardness iii) Friability iv) Disintegration time v) Dissolution rate

Content of Active Ingredient

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 50 mg of the medicament was taken into a boiling test tube and extracted with 4 x 10 ml quantities of methanol. The methanolic extracts were collected into 50 ml volumetric flask and the volume was made up to 50 ml with methanol. The solution was subsequently diluted with phosphate buffer of pH 6.8 in the case of Efnodipine.

Hardness

Hardness of the tablets was tested using a Monsanto hardness tester.

Friability

Friability of the tablets was determined in a Roche friabilator.

Disintegration Time

Disintegration times were determined in thermonic tablet disintegration test machine using distilled water as fluid.

Dissolution Rate Study

The dissolution rate of medicament from the tablets prepared was studied in phosphate buffer of pH 6.8 (900 ml) in the case of Efnodipine tablets using Dissolution 2000 (Labindia) 8-station dissolution test apparatus with a paddle stirrer at 50 rpm. A temperature of 37°C ± 1°C was maintained throughout the study. One tablet was used in each test. Sample of dissolution media (5 ml) were withdrawn through a filter (0.45µ) at different intervals of time, suitably diluted and assayed for Efnodipine tablets at 250nm. The sample of dissolution fluid withdrawn at each time was replaced with fresh fluid and a suitable correction was made for the amount of drug lost in the samples in calculating the percent drug dissolved. The dissolution experiments were replicated four times each (n=4).

Table 1: Formulae of Efnodipine Tablets Prepared Employing βCD and Kolliphor HS15as per 2^2 Factorial Design

Ingredient (mg/tab)	FORMULATION			
	E1(F_1)	E2(F_a)	E3(F_b)	E4(F_{ab})
Efnodipine	40	40	40	40
βCD	-	80	-	80
Kolliphor HS15	-	-	2	2
Cross Carmellose Sodium	11.5	11.5	11.5	11.5
PVP	4.6	4.6	4.6	4.6
Talc	4.6	4.6	4.6	4.6
Magnesium stearate	4.6	4.6	4.6	4.6
Lactose	164.7	84.7	162.7	82.7
Total weight (mg)	230	230	230	230

Table 2: Formulae of Efnodipine Tablets Prepared Employing HPβCD and Kolliphor HS15as per 2^2 Factorial Design

Ingredient (mg/tab)	FORMULATION			
	E1(F_1)	E2(F_a)	E3(F_b)	E4(F_{ab})
Efnodipine	40	40	40	40
HβCD	-	80	-	80
Kolliphor HS15	-	-	2	2
Cross Carmellose Sodium	11.5	11.5	11.5	11.5
PVP	4.6	4.6	4.6	4.6
Talc	4.6	4.6	4.6	4.6
Magnesium stearate	4.6	4.6	4.6	4.6
Lactose	164.7	84.7	162.7	82.7
Total weight (mg)	230	230	230	230

Table 3: Hardness, Friability, Disintegration Time and Drug Content of Efnodipine Tablets Formulated employing βCD and Kolliphor HS15

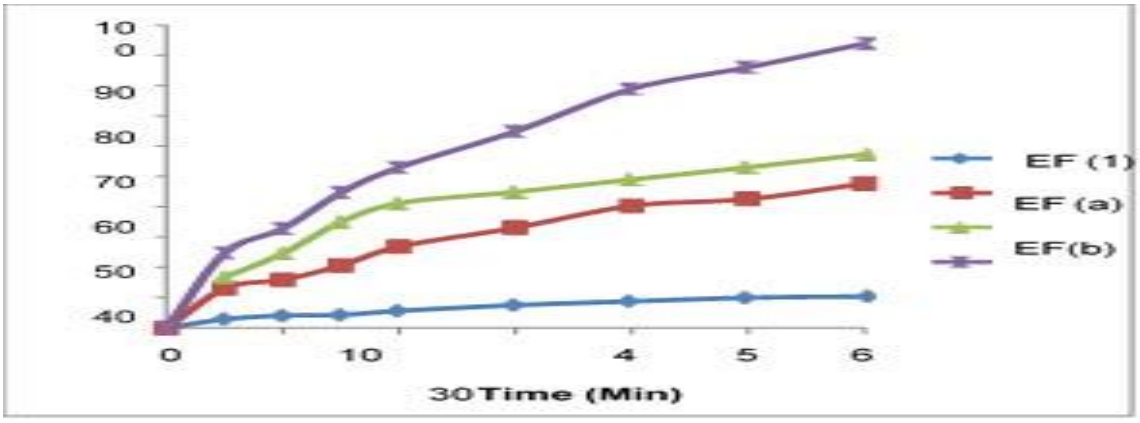
Formulation(code as per 2^2 –Factorial Design)	Hardness(kg/sq.cm)	Friability (%)	Disintegration Time (min.)	Efnodipine content (Percent)
E1(1)	6.5	0.65	2.5	99.5
E2(a)	7.0	0.75	2.0	98.6
E3(b)	7.0	0.40	1.0	100.2
E4(ab)	6.5	0.80	1.0	98.8

Table 4: Hardness, Friability, Disintegration Time and Drug Content of Efnodipine Tablets Formulated employing HPβCD and KolliphorHS15

Formulation(code as per 2^2 – Factorial Design)	Hardness(kg/sq.cm)	Friability (%)	Disintegration Time (min.)	Efnodipine content (Percent)
E5(1)	7.0	0.85	3.0	99.6
E6(a)	7.5	0.60	2.5	98.4
E7(b)	6.0	0.55	1.5	100.5
E8(ab)	7.5	0.45	1.5	98.4

Table 5: Dissolution Profiles of Efnodipine Tablets Formulated Employing BCD and Kolliphor HS15as Per 2^2 Factorial Design

Time min	Percent Efnodipine dissolved (x± sd)			
	E1(1)	E2(a)	E3(b)	E4(ab)
5	2.92±0.221	13.15±0.550	16.80±1.07	24.8±0.496
10	4.10±0.141	15.90±0.529	24.06±0.496	32.85±0.251
15	4.35±0.173	20.65±0.750	35.01±0.938	44.75±1.112
20	5.65±0.310	26.87±0.25	41.22±0.531	53.05±0.66
30	7.55±0.288	33.10±0.871	44.92±1.268	64.95±0.68
40	8.82±0.330	40.32±0.32	49.02±1.040	78.95±1.268
50	10.0±0.355	42.57±1.04	53.07±0.899	86.10±0.547
60	10.45±0.191	47.67±0.822	57.35±0.826	93.90±0.697



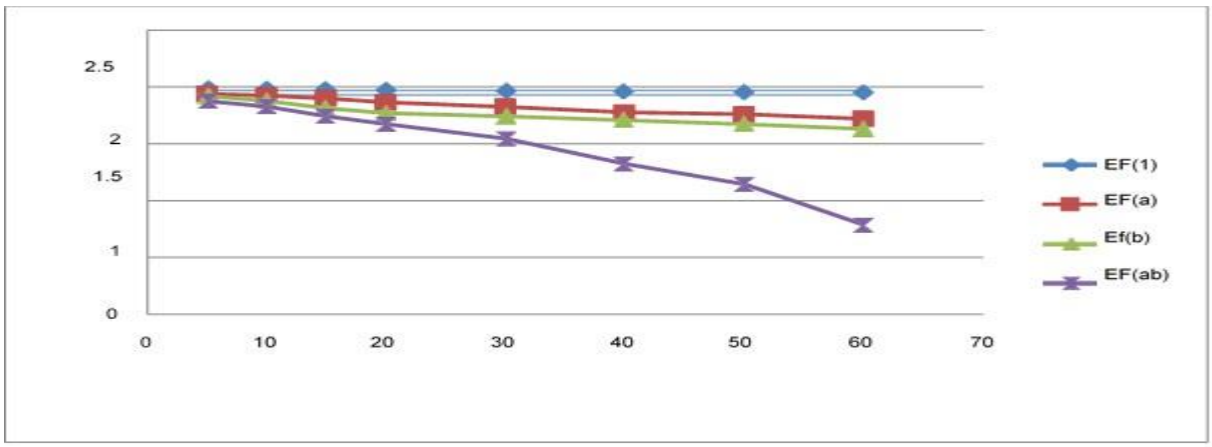
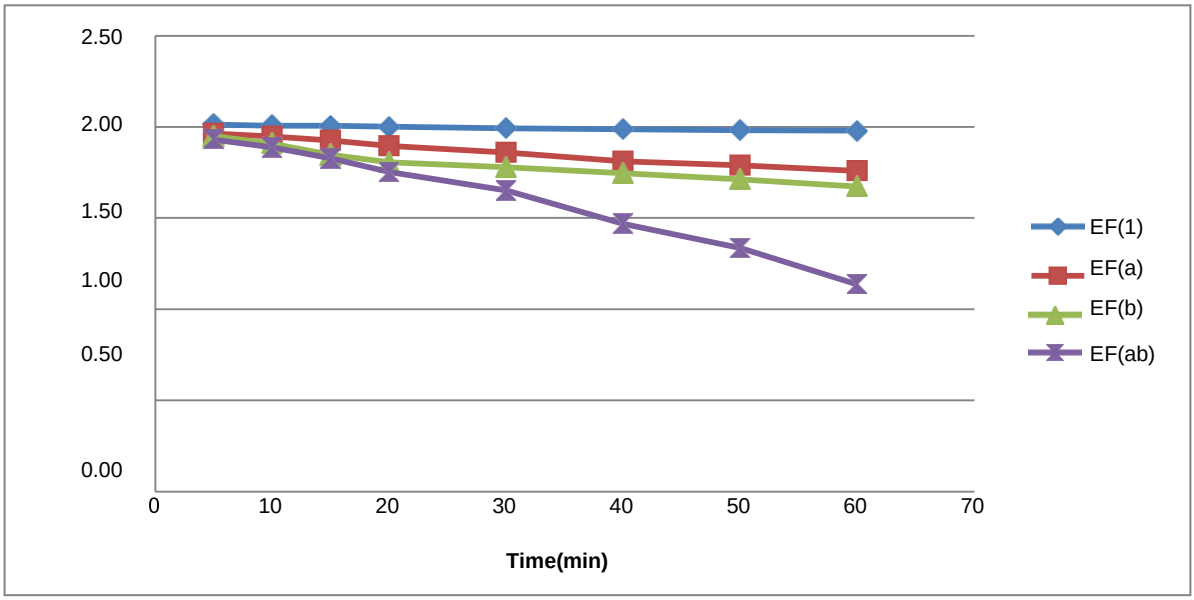


Table 6: Dissolution Profiles of Efnodipine Tablets Formulated Employing HBCD and Kolliphor HS15as Per 2^2 Factorial Design

Time min	Percent Efnodipine dissolved (x± sd)			
	E5(1)	E6(a)	E7(b)	E8(ab)
5	2.92±0.221	13.62±0.403	16.80±1.07	20.6±0.832
10	4.10±0.141	16.95±0.435	24.60±0.496	28.52±0.573
15	4.35±0.173	21.32±1.370	35.0±0.938	38.15±0.90
20	5.65±0.310	26.82±1.230	41.22±0.531	48.45±0.597
30	7.55±0.288	32.97±0.531	44.92±1.268	59.62±1.09
40	8.82±0.330	40.40±0.938	49.03±1.04	74.07±1.25
50	10.0±0.355	43.45±1.340	53.07±0.899	81.23±0.72
60	10.45±0.191	47.45±1.398	57.35±0.826	88.4±0.748



RESULTS AND DISCUSSION

The post compression parameters such as hardness, friability, thickness, disintegration time, and drug content are shown in Table 3 and Table 4. In all the formulations, the hardness test indicates good mechanical strength. Friability of all formulations was less than 1%, which indicated that the tablets had a good mechanical resistance. Drug content was found to be high (≥101.00 %) and uniform in all the formulations. The important parameter that requires to be optimized in the development of the fast-disintegrating tablets is the disintegration time of the tablets. In the present investigation, all the tablets disintegrated in ≤100 seconds fulfilling the official requirements (<3 min.) for disintegrating tablets[12]. The absorption of water is an important step for the subsequent disintegration process of tablets[13].Bi et. al.[14]have reported that when higher concentration of super disintegrants were added to the tablet formulation, they absorbed considerable amount of water and resulted in increase in viscosity of fluid within the tablet mass. This delayed further water penetration into the tablets. Therefore, it was decided to use super disintegrants concentrations only up to 5% w/w.

Drug-CD and Drug-CD-Kolliphor HS15complex systems could be formulated into compressed tablets by wet granulation method. The hardness, friability, drug content and disintegration time of the tablets prepared are given in Tables 3,4 . Hardness of the tablets was in the range 6.0 –7.5 kg/sq.cm. Percent weight loss in the friability test was less than 0.85% with all the formulations. The disintegration time was in the range 1 –3.5 min. with all the tablets prepared. Drug content of the tablets was within100 ± 2% of the labeled claim.

Dissolution Rate Characteristics of Efnodipine Tablets

Dissolution of Efnodipine from all the prepared tablets was studied in phosphate buffer of pH 6.8. The dissolution profiles of the Efnodipine tablets prepared and shown in Fig.1,2. Dissolution data were analyzed as per zero and first order kinetics. The coefficient of determination (R2) values in the analysis of dissolution data indicated that the dissolution of Efnodipine from all the tablets formulated followed first order kinetics. The first order dissolution plots are shown in Figs 1,2. The first order dissolution rate (K1) values along with dissolution efficiency (DE30) values of various Efnodipine tablets prepared are given in Tables 5,6. Tablets formulated employing CDs and Kolliphor HS15 gave relatively higher rates (K1) of dissolution and dissolution efficiency (DE30) values when compared to those of Efnodipine plain tablets (i.e., tablets formulated employing Efnodipine alone). The order of increasing dissolution rate (K1) observed with various Efnodipine tablets wasE1(plain) <E2 (βCD) = E6 (HPβCD)<E3 (Kolliphor HS15) <E8 (HP βCD-Kolliphor HS15) <E4 (βCD-Kolliphor HS15). Formulations E4 and E8, which are formulated employing βCD-Kolliphor HS15and HPβCD-Kolliphor HS15 respectively, gave much higher dissolution rates when compared to plain tablets, E1. A 42.5 and 34.2 fold increase in K1was observed respectively with formulations E4 and E8 when compared to formulation E1 (plain tablets). The dissolution efficiency (DE30) was also increased from 4.56% for formulation E1 to 41.54 % and 36.59 % respectively for formulations E4 and E8.

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