Research Article

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

S.K.Sathish[1*], Dr. V.P. Pandey[2]
[1] Department of Pharmaceutics, Ultra College of Pharmacy, Madurai, Tamil Nadu, India.
[2]Department of Pharmacy, Annamalai university, Annamalai nagar, Chidambaram, Tamil Nadu, India.
***Corresponding author's E-mail:** krrs78@gmail.com

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ABSTRACT

Azelnidipine, a calcium channel blocker, is used for hypertension and angina pectoris. Azelnidipine 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 Azelnidipine. The individual main effects and combined (interaction) effects of cyclodextrins and surfactants on the solubility and dissolution rate of Azelnidipine was evaluated in a series of 22 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 Azelnidipine tablets can be prepared by kneading method using super disintegrants.

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

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INTRODUCTION

Hypertension is the most common chronic disease and the calcium channel antagonist is the most popularly used antihypertensive drug. Azelnidipine is a third generation and long-acting dihydropyridine calcium channel antagonist[1]. A series of research has demonstrated that azelnidipine produced an effective antihypertensive effect in patients with essential hypertension. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules, one important drawback of this dosage form for some patients is the difficulty to swallow[2]. Mouth dissolving tablets provide an advantage, particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. Mouth dissolving of tablet results in quick dissolution and rapid absorption, which provide rapid onset of action. Moreover, a drug candidate that undergoes pre-gastric absorption when formulated as mouth dissolving tablets may show increased oral bioavailability[3]. It provides good stability, accurate dosing, and easy manufacturing.

Azelnidipine is a vasodilator that induces a gradual decrease in blood pressure in hypertensive patients. Unlike other members of its drug class, azelnidipine does not induce reflex tachycardia due to vasodilation. This is likely due to the fact that it elicits a gradual fall in blood pressure. It also exhibits a prolonged hypotensive effect and has been shown to have a strong anti-arteriosclerotic action in vessels due to its high affinity for vascular tissue and antioxidative activity[4]. Clinical studies have demonstrated that azelnidipine markedly reduced heart rate and proteinuria in hypertensive patients by inhibiting sympathetic nerve activity. Azelnidipine has also been confirmed to have cardio-protective, neuroprotective, and anti-atherosclerotic properties, and has also been found to prevent insulin resistance[5] ·Azelnidipine inhibits trans-membrane Ca2+ influx through the voltage-dependent channels of smooth muscles in vascular walls. Ca2+ channels are classified into various categories, including L-type, T-type, N-type, P/Q-type, and R-type Ca2+ channels. The L-type Ca2+ channels [6]. Normally, calcium induces smooth muscle contraction, contributing to hypertension. When calcium channels are blocked, the vascular smooth muscle does not contract, resulting in relaxation of vascular smooth muscle walls and decreased blood pressure.

Mouth dissolving tablets are designed to be placed in mouth allowed to dissolve in the saliva and then swallowed without the aid of water[7-9]. The objective of the present

investigation was to develop fast disintegrating. The major objective is to enhance the immediate onset of action in a shorter period of time with improved bioavailability, solubility, dissolution rate. Azelnidipine 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 Azelnidipine tablets with enhanced dissolution rate and dissolution efficiency employing drug-CD-surfactant complex systems.

MATERIALS AND METHODS

Azelnidipine 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 HS15 Complexes as per a 2^2–Factorial Study: Tablet of Azelnidipine (16mg) 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.

Preparation of Tablets

Tablet of Azelnidipine (16mg) were prepared by wet granulation method as per the formulae given in Tables 1-2.

Azelnidipine Tablets with βCD and Kolliphor HS15

Statistical code as per 2^2–Factorial Design	Description	Formulation code
1	Tablets of Azelnidipine alone	A1
a	Tablets of Azelnidipine -βCD (1 : 2) inclusion complex	A2
b	Tablets of Azelnidipine - Kolliphor HS15 (5%) blend	A3
ab	Tablets of Azelnidipine βCD-Kolliphor HS15(1 : 2 : 0.05) ternary complexes	A4

Azelnidipine Tablets with HPβCD and Kolliphor HS15

Statistical code as per 2^2– Factorial Design	Description	Formulation code
1	Tablets of Azelnidipine alone	A5 Same as A1
a	Tablets of Azelnidipine - HβCD (1 : 2)inclusion complex	A6
b	Tablets of Azelnidipine - Kolliphor HS15(5%) blend	A7 Same as A3
ab	Tablets of Azelnidipine - HβCD- Kolliphor HS15(1 : 2 : 0.05) ternary complexes	A8

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 Azelnidipine.

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 Azelnidipine 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 Azelnidipine 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 Azelnidipine Tablets Prepared Employing βCD and Kolliphor HS15as per 2^2 Factorial Design

Ingredient (mg/tab)	FORMULATION			
	A1(F_1)	A2(F_a)	A3(F_b)	A4(F_{ab})
Azelnidipine	16	16	16	16
βCD	-	31.6	-	32
Kolliphor HS15	-	-	1	1
Croscarmellose Sodium	10.3	10.3	10.3	10.3
PVP	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5	2.5
Lactose	42.5	10.9	41.5	9.5
Total weight (mg)	76.3	76.3	76.3	76.3

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

Ingredient (mg/tab)	FORMULATION			
	A1(F_1)	A2(F_a)	A3(F_b)	A4(F_{ab})
Azelnidipine	16	16	16	16
HβCD	-	31.6	-	31.2
Kolliphor HS15	-	-	6	6
Cross Carmellose Sodium	10.5	10.5	10.5	10.5
PVP	3.7	3.7	3.7	3.7
Talc	3.7	3.7	3.7	3.7
Magnesium stearate	3.7	3.7	3.7	3.7
Lactose	38.7	7.1	31.7	1.5
Total weight (mg)	76.3	76.3	76.3	76.3

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

Formulation(code as per 2^2 –Factorial Design)	Hardness(kg/sq.cm)	Friability (%)	Disintegration Time (min.)	Azelnidipine content (Percent)
A1(1)	7.2	0.51	3.2	99.6
A2(a)	6.7	0.60	1.8	94.6
A3(b)	6.1	0.42	1.2	99.7
A4(ab)	7.1	0.77	0.8	98.5

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

Formulation(code as per 2^2 –Factorial Design)	Hardness(kg/sq.cm)	Friability (%)	Disintegration Time (min.)	Azelnidipine content (Percent)
A5(1)	7.1	0.81	3.5	99.9
A6(a)	7.4	0.68	2.4	95.4
A7(b)	6.3	0.52	1.7	98.5
A8(ab)	7.2	0.47	1.9	94.3

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

Time min	Percent Azelnidipine dissolved (¯x± sd)			
	A1(1)	A2(a)	A3(b)	A4(ab)
5	4.22±0.763	13.60±0.783	17.85±0.660	26.65±1.55
10	6.32±0.427	16.77±0.303	27.05±0.519	35.05±0.465
15	7.80±0.424	23.32±0.780	35.35±0.785	46.15±0.55
20	9.40±0.673	29.27±0.780	42.25±0.465	56.35±0.613
30	11.30±0.912	35.07±0.607	47.05±0.723	67.60±0.588
40	12.57±0.531	42.92±1.28	51.27±0.788	82.60±1.641
50	14.62±1.078	44.32±0.921	54.50±1.35	86.90±1.248
60	15.65±0.866	46.87±0.75	56.82±0.44	93.12±2.203

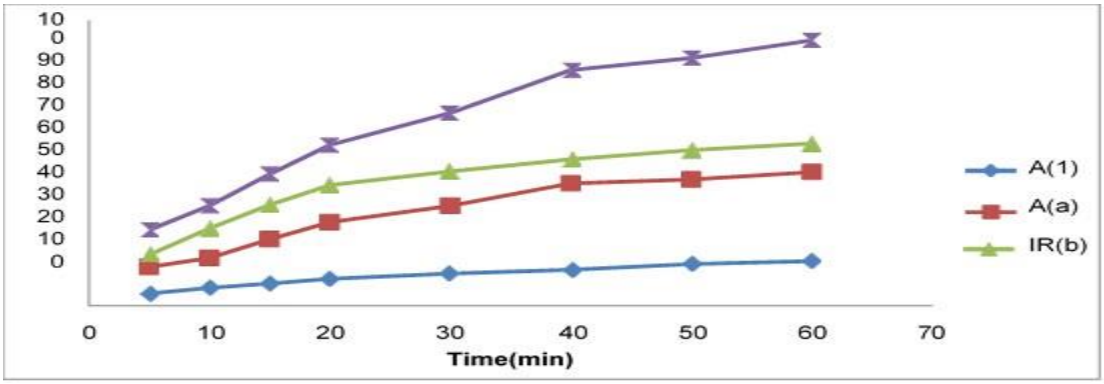

Figure 1: Dissolution Profiles of Azelnidipine tablets formulated employing βCD and Kolliphor HS15 as per 2^2 Factorial Design

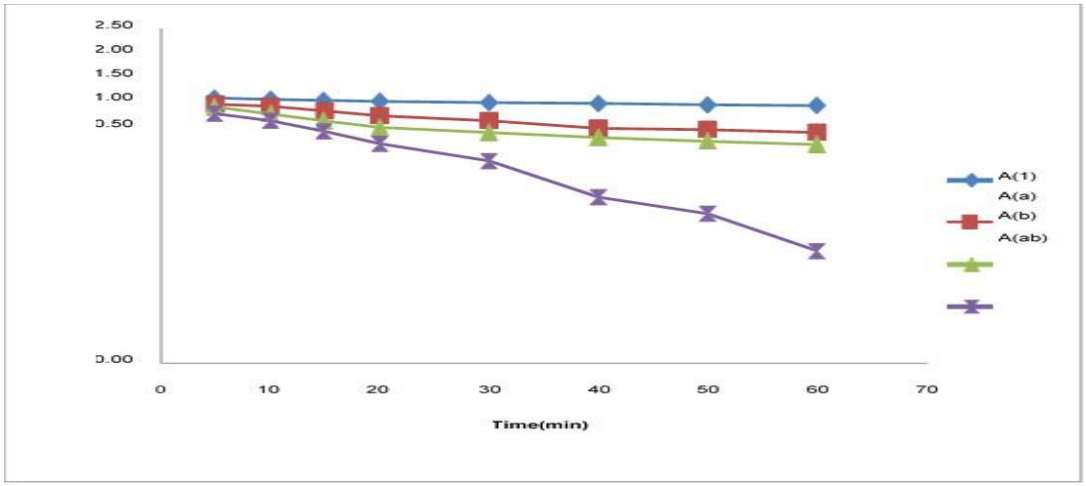

Figure 2: First Order Dissolution Profiles of Azelnidipine tablets formulated employing βCD and Kolliphor HS15 as per 2^2 Factorial Design

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

Time (min)	Percent Azelnidipine Dissolved ($\bar{x}$ ± sd)			
	Ir5 (1)	Ir6 (a)	Ir7 (b)	Ir8(ab)
5	4.22±0.763	15.02±0.623	17.85±0.660	21.3±0.808
10	6.32±0.427	18.85±0.479	27.05±0.519	30.25±0.619
15	7.80±0.424	21.9±1.122	35.35±0.785	40.92±1.335
20	9.40±0.673	28.22±0.967	42.25±0.465	52.92±2.168
30	11.3±0.912	34.80±0.637	47.05±0.723	64.47±1.386
40	12.57±0.531	42.92±0.525	51.27±0.788	76.42±4.598
50	14.62±1.078	45.30±0.883	54.50±1.35	82.27±2.725
60	15.65±0.866	46.87±0.809	56.82±0.44	86.92±1.284

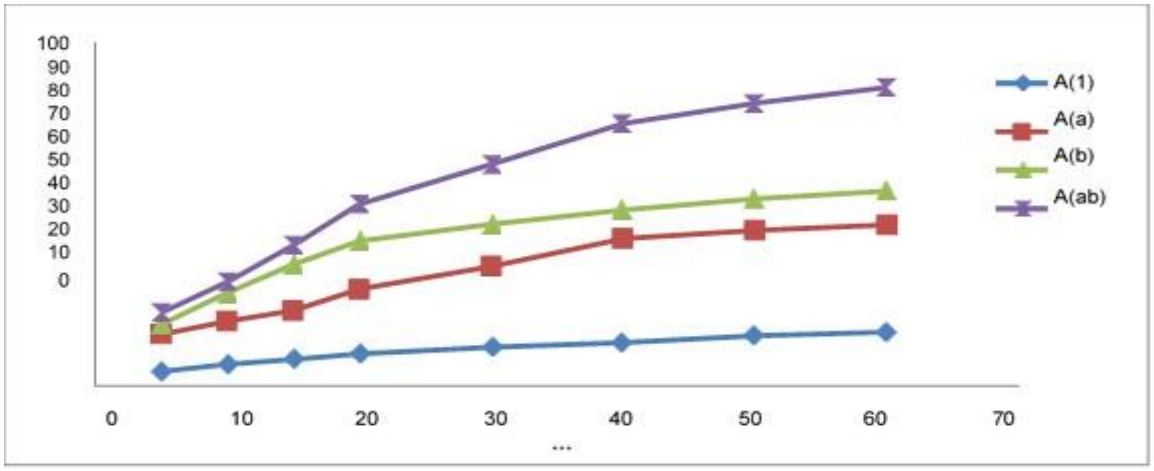

Figure 3: Dissolution Profiles of Azelnidipine tablets formulated employing HPβCD and Kolliphor HS15 as per 2^2 Factorial Design

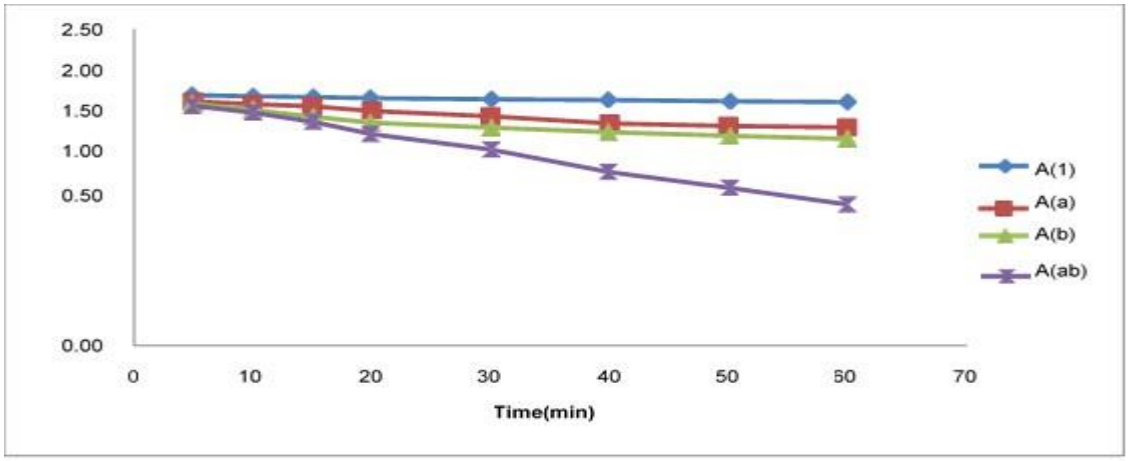

Figure 4: First Order Dissolution Profiles of Azelnidipine tablets formulated employing βCD and Kolliphor HS15 as per 2^2 Factorial Design

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[10]. The absorption of water is an important step for the subsequent disintegration process

of tablets[11].Bi et. al.[12]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 Azelnidipine Tablets

Dissolution of Azelnidipine from all the prepared tablets was studied in 0.1N hydrochloric acid. The dissolution profiles of the Azelnidipine tablets prepared are given in Table 7.23– 7.24 and in Fig. 7.5-7.8. Dissolution data were analyzed as per zero and first order kinetics. The coefficient of Determination (R^2) values in the analysis of dissolution data indicated that the dissolution of Azelnidipine from all the tablets formulated followed first order kinetics. The coefficient of Determination (R^2) values were in the range 0.8927-0.9978 with all the Azelnidipine tablets prepared. The first order dissolution plots are shown in Figs. 2 and 4. The first order dissolution rate (K_1) values along with dissolution efficiency (DE_{30}) values of various Azelnidipine tablets prepared .Tablets formulated employing CDs and Kolliphor HS15 gave relatively higher rates (K_1) of dissolution and dissolution efficiency (DE_{30}) values when compared to the Azelnidipine plain tablets (i.e. tablets formulated with Azelnidipine alone). The order of increasing dissolution rate (K_1) observed with various Azelnidipine tablets was A1 (plain) < A2 (βCD)= A6 (HPβCD) < Ar3 (Kolliphor HS15) < A8 (HP βCD-Kolliphor HS15) <A4 (βCD-Kolliphor HS15) Formulations A4 and A8, which are formulated employing βCD-Kolliphor HS15 and HPβCD-Kolliphor HS15 respectively, gave much higher dissolution rates when compared to plain tablets, A1. A 21.35 and 16.85 fold increase in K_1 was observed respectively with formulations A4 and A8 when compared to formulation A1 (plain tablets). The dissolution efficiency (DE_{30}) was also increased from 7.29% for Formulation A1 (plain tablets) to 43.32 % and 39.36 % respectively for formulations A4 and A8.

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