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Original Research Article

DEVELOPMENT AND EVALUATION CILNIDIPINE FAST DISSOLVING TABLET BY USING ISAPGHULA HUSK AS NATURAL SUPERDISINTEGRANT

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Abstract

Objective: In the present reported project study, the effect of Natural superdisintegrant was compared with synthetic Superdisintegrants and conventional Superdisintegrants in the Fast-Dissolving tablet formulation of Clinidipine. Cilnidipine is the novel dihydropyridine calcium antagonist and calcium antagonistic activity of clinidipine is long lasting than those of Nifedipine and Nicardipine. Cilnidipine has been used for the treatment of any hypertension and hypertensive-associated vascular disorders. Cilnidipine shows a very low solubility (BCS Class-II drug Low solubility high permeability) and compliance to the medication is always very poor. The dissolution rate is directly proportional to solubility of drug. Methods: In the present work, 9 formulations of Fast Dissolving tablets of Clinidipine were prepared by using natural Superdisintegrants was evaluated and compiles with the official standards, parameters and specifications. Various formulations were prepared using three types of different superdisintegrant namely- Isapghula Husk, sodium starch glycolate, Crospovidone sodium with three concentrations (2%, 4%, 6%) by direct compression method. Result: The blend was evaluated for pre-compression parameters like Angle of repose, bulk density, tapped density, and then tablet evaluated post-compression parameters like thickness, drug content, hardness, weight variation, wetting time, friability, disintegration time, dissolution time, drug release study. Formulation ST8 showed the lowest disintegration time and in-vitro dissolution studies recorded that formulation ST showed better drug release at the end of 3 minutes. Conclusion: The best formulations were also found to be stable and optimized formulations were subjected to the stability studies as per ICH guideline and standards.

Keywords: Fast Dissolving tablet, Clinidipine, Co-proceed, sodium starch glycolate, Natural, Isapghula Husk direct compression, dissolution time

INTRODUCTION

The tablet is most widely used dosage for because of its convenience in term of self-administration, compactness, accurate drug dose and ease in manufacturing. Over this one drawback of conventional tablet is difficulty in swallowing by paediatric and geriatric patients.[1-2] To beat these issues the scientists have developed novel drug delivery system that known as Fast Dissolving tablet. The Fast Dissolving defined as the tablets that dissolve in few seconds in the mouth when they come with

contact saline without requirement of additional water. The advantage of FDT is onset of action, higher patient acceptance, and increased bioavailability.[3-4] Cilnidipine is a novel and unique dihydropyridine calcium channel blocker that possesses a slow-onset, long-lasting vasodilating effect. It is a 4th generation dihydropyridine (DHP) type of calcium channel antagonist. Unlike other calcium channel antagonists, cilnidipine has dual action blocks the influx of Ca2+ ions into both vascular smooth muscles at the level of L-type Ca2+ channels and neuronal cells at the level of N-type Ca2+ channels. Bioavailability of Clinidipine is about 80% to 90% and its half-life is 4-4.5 h. The drug is distributed throughout the body and 90% of drug binds to plasma proteins. It undergoes rapid first-pass metabolism in the liver (approximately 95% of a dose). This leads to lower bioavailability of Clinidipine. In order to overcome such extensive first-pass metabolism effect, so the drug is selected for Fast Dissolving tablet.[5-9]

MATERIAL AND METHOD: -

MATERIAL: -

Cilnidipine was a gift sample from Emcure Pharmaceuticals Pvt. Ltd. Pune, Isapghula Husk was gifted by Krishna Herbals, Delhi, Aspartame used was procured from Sweetener India, Delhi, and other reagents and chemicals used were of analytical grade.

METHOD: -

Fast Dissolving tablets of Clinidipine were prepared by direct compression method. Pure API drug and excipients were passed through # 60 No. mesh. Required amount of drug and excipients were taken for every formulation according Table No. 1. The powdered pure drug, Mannitol and Lactose were mixed uniformly with continuous triturating using mortar and pestle. Then required quantity of super disintegrates and aspartame taken for each formulation and mixed, finally magnesium stearate and talc powder were added and mixed well.[10-12] The mixed blend of drug and excipients were compressed by using 7 station tablet punching machine. (Shakti pharmaceuticals**)** 4 Mm punch. A Batch of 100 tablets of each formulation were prepared for all the designed formulation. Before the tablet preparation punch the mixture blend of all designed formulations were subjected to compatibility studies (IR) and pre-compression parameters like- Angle of repose, Bulk density, Tapped density, compressibility index, Hauser's ratio.[13-15]

Pre-formulation studies: -

Angle of Repose (θ):

Angle of repose is the maximum possible angle between the surface of the pile of the powder and the horizontal plane of the powder. When more quantity powder is added to the pile, it slides down, until the mutual friction of the particles producing a surface angle θ, is equilibrium with the gravitational force.[15-17]

The angle of repose was determined by the funnel method suggested by the scientist Newman. Angle of repose is determined by the following formula

$\tan \theta = h/r$

$\theta = \tan^{-1} h/r$ Where θ = Angle of repose, r = Radius of the cone, h = height of the cone

Bulk Density:

Density is weight mass per unit volume. Bulk density is defined as the mass of the powder is divided by the bulk volume of powder and is expressed as gm/ cm^3.The bulk density of a powder primarily depends on its, particle shape, particle size, distribution and the tendency of particles to adhere together. There are two types of bulk density.[18-19]

Low bulk density

The particles are pack in such a way so as to leave large gaps between their surfaces resulting up in light powder of low bulk density.

High bulk density

Here the smaller particles shift between the large particles resulting in heavy powder of high bulk density

Tapped Density (DT):

It was the ratio of total mass of the powder to tapped volume of the powder. Volume was reported by tapping the powder for 500 times and the tapped volume was observed, if the difference between these two volumes was less than 2%. If it more than 2%, then tapping was continued for 750 times and tapped volume was noted. Tapping was continued until the difference between volumes was less than 2% in bulk density apparatus. It was expressed in g/ml and was given as following,

DT= M/Vt

Where, M is the mass of powder

Vt is the tapped volume of the powder.[22-24]

Carr's index (or) % compressibility:

Carr's index indicates powder flow properties. It is expressed by percentage and is given by:

I=DT−Db/DT×100

Where, DT denotes the tapped density of the powder

And Db is the bulk density of the powder.[25-28]

Hausner ratio:

Hausner ratio is an indirect index of ease of powder flow properties. It is calculated by the following formula:

Hausner ratio=Dt/Db

Where, Dt show the tapped density., Db is the bulk density.

Lower hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25)

EVALUATATION OF TABLET: -

All prepared tablets of Clinidipine were evaluated for the following parameters as per IP guideline and standards for all the calculations are represented in the table No.3

Weight Variation: -

Twenty tablets of Clinidipine formulation were selected randomly from each of the formulation and weighted individually using Windsar Digital Balance for their weight variation data. The average weight of the tablets as well as percentage deviation was calculated.[29-31]

Hardness: -

Hardness of the Clinidipine tablets were measured with Monsanto tablet hardness tester for evaluation the hardness of the tablets.

Thickness: -

The thickness of the tablet was measured in mm by the Vernier Calipers for all the designed formulation batches.

Friability: -

The Friability of the Clinidipine tablet by a sample of twenty tablets was measured using USP type Roche Friabilator. The tablets were dusted reweighed and percentage weight-loss was calculated.

%Friability= Initial Weight−Final Weight * 100/ Initial Weight

Water absorption ratio:

A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in small Petri-plate (ID = 6.5 cm) containing 10 ml of water. A tablet was placed on the paper and time for complete wetting of the tablet was measured in seconds. Three trials for each batch were performed and the standard deviation was also determined. The wetted tablet was weighed and water absorption ratio R, was determined by following equation

$$\mathbf{R = \{(Wa - Wb) / Wa\} \times 100}$$

Where, Wa and W_b were weights of the tablets after and before study.[33-35]

Wetting Time

A piece of tissue paper (12cmX10.75cm) folded twice was placed in a small Petri dish (ID = 9 cm) containing 5ml pH 6.8 phosphate buffer, A tablet was placed on the paper and the time taken for complete wetting was observed. Three tablets from

each formulation were randomly selected and the average wetting time was noted.

DISINTEGRATION STUDY: -

Disintegration time study was carried out by selecting 6 tablets of Clinidipine and performed disintegration test (Lab India) using 900 ml distilled water at temperature ($37^0C \pm 2^0C$). [36-37]

DISSOLUTION STUDY: -

The In-vitro for the dissolution study was carried out in the USP (United state pharmacopeia) dissolution test apparatus type II known as Paddle dissolution apparatus, used phosphate buffer as dissolution medium as 900 ml containing PH 6.8 was taken in vessel and the temperature maintained at 37 ± 0.5^0C. The speed of the paddle was set at RPM 50, then 5 ml dissolution medium was withdrawn and the same amount (5ml) of fresh medium was replenished to the dissolution medium. The calculations of the Concentration were calculated by absorbance base. The release of the drug was performed in replicates of three.[38]

Table 1: Formulation of Fast Dissolving tablet of Clinidipine:

Ingredients(mg)	**ST1**	**ST2**	**ST3**	**ST4**	**ST5**	**ST6**	**ST7**	**ST8**	**ST9**
Clinidipine	20	20	20	20	20	20	20	20	20
Crosspovidone	2	4	6	-	-	-	-	-	-
SodiumStarch Glycolate	-	-	-	2	4	6	-	-	-
Isapghula Husk	-	-	-	-	-	-	2	4	6
Aspartame	2	2	2	2	2	2	2	2	2
Flavour	2	2	2	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Mannitol	40	40	40	40	40	40	40	40	40
Lactose	30	28	26	30	28	26	30	28	26
TOTAL	100	100	100	100	100	100	100	100	100

Table 2: Pre-compression parameters of Clinidipine Fast Dissolving tablet

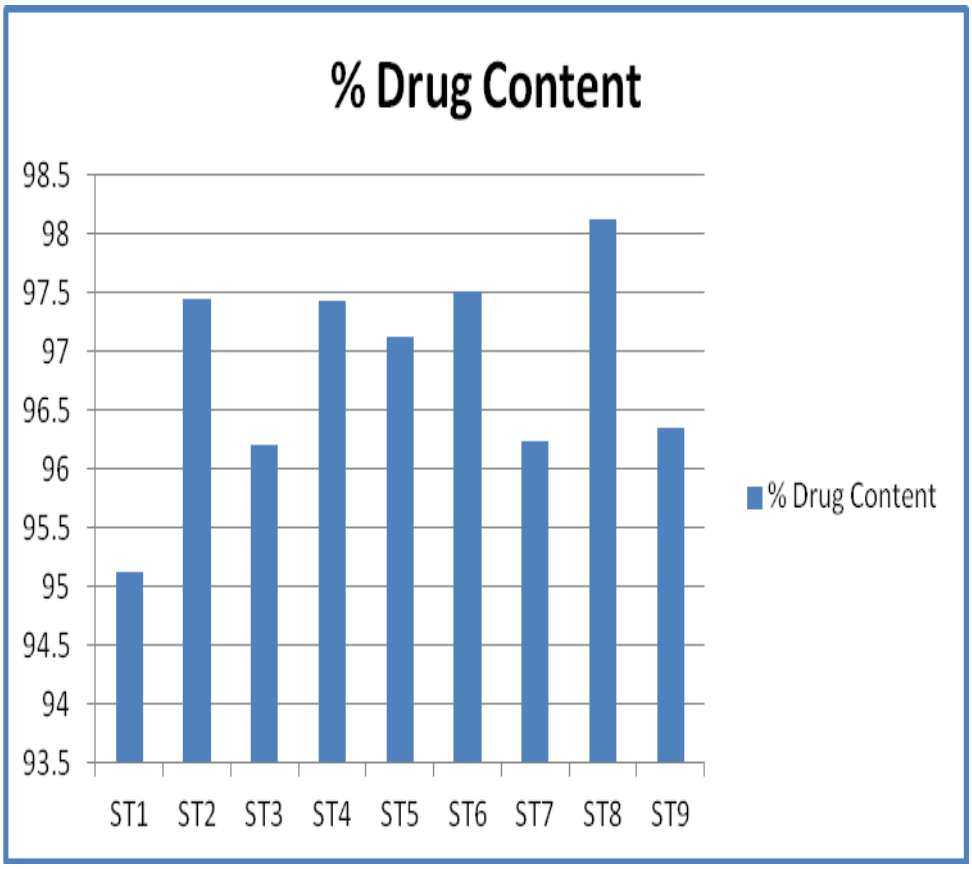
Parameters / Formulation	Bulk Density (mg/ml)	Tapped Density (mg/ml)	Hausners Ratio	Compressibility Index (%)	Angle of Repose
ST1	0.389± 0.01	0.514±0.02	1.32±0.02	24.31± 0.02	20.43± 0.02
ST2	0.395± 0.03	0.529±0.01	1.32±0.01	24.61± 0.01	20.66± 0.03
ST3	0.394± 0.02	0.513±0.03	1.30±0.02	23.19± 0.02	20.22± 0.01
ST4	0.402± 0.04	0.488±0.02	1.21±0.03	17.62± 0.01	21.86 ± 0.03
ST5	0.415± 0.09	0.491±0.03	1.18±0.01	15.47± 0.03	21.11 ± 0.02
ST6	0.421± 0.03	0.489± 0.04	1.16±0.01	13.90± 0.02	20.44 ± 0.01
ST7	0.388± 0.06	0.494± 0.01	1.27±0.01	21.45± 0.01	23.09± 0.02
ST8	0.391± 0.05	0.495± 0.03	1.26±0.04	21.01± 0.03	24.61± 0.01
ST9	0.393± 0.02	0.499± 0.04	1.26±0.01	21.24± 0.01	22.04± 0.02

Table 3: Post-Compression parameters of Clinidipine Fast Dissolving tablet:

Parameters / Formulation	Thickness (mm)	Weight (mg)	Hardness (Kg/cm^2)	Friability (%)	Disintegration Time (Sec)	Swelling Time (Sec)
ST1	4	96.05±0.55	3.05±0.05	0.55±0.04	45±0.01	22±1
ST2	4	97.57±0.78	3.02±0.01	0.58±0.05	45±0.02	20±2
ST3	4	97.01±0.11	3.25±0.04	0.59±0.07	42±0.01	21±1
ST4	3	96.02±0.25	3.24±0.02	0.61±0.06	45±0.02	20±1
ST5	3	98.01±0.11	3.22±0.01	0.62±0.02	34±0.03	18±2
ST6	3	100.05±0.15	3.23±0.03	0.64±0.02	40±0.01	20±2
ST7	4	102.01±0.15	3.32±0.05	0.65±0.03	44±0.02	22±2
ST8	4	101.50±0.04	3.40±0.04	0.63±0.04	42±0.03	21±2
ST9	4	102.02±0.22	3.45±0.03	0.58±0.06	43±.0.04	22±1

Table No. 4:- Drug Content in the Fast Dissolving Tablet of Clinidipine:

Parameters / Formulation	Drug Content (mg per Tablet)	% Drug Content
ST_1	95.12±0.015	95.12
ST_2	97.44±0.009	97.44
ST_3	96.21±0.015	96.21
ST_4	97.03±0.010	97.43
ST_5	97.12±0.025	97.12
ST_6	97.51±0.021	97.51
ST_7	96.23±0.018	96.23
ST_8	98.12±0.015	98.12
ST_9	96.35±0.012	96.35



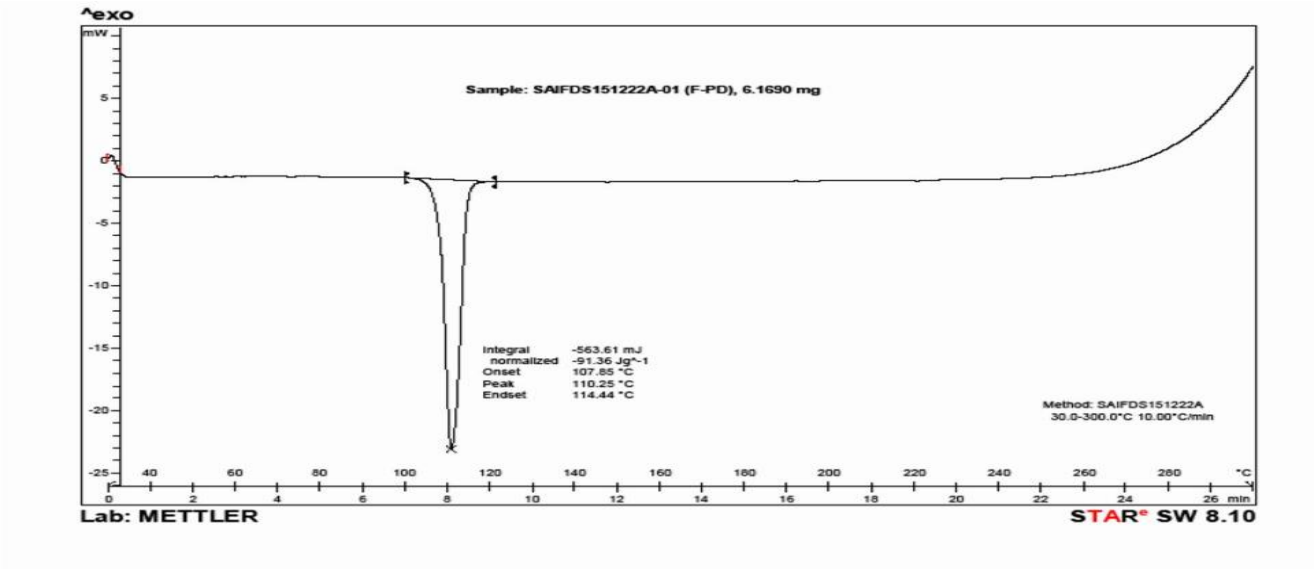


Figure.2: DSC Thermogram of Clinidipine

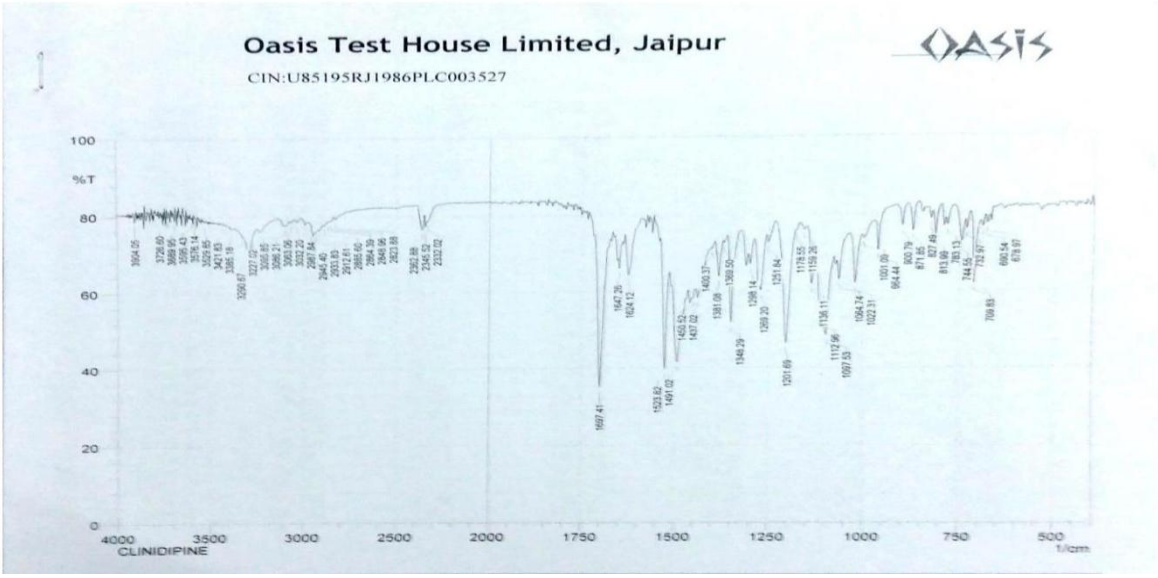


Figure.3: IR Spectra of Clinidipine

RESULTS:

Bulk Density and Tapped Density of the Blend were found in standard range as per IP guidelines.Carr's index of the prepared blend fall in the range of 13.90 to 24.61% and this is also supported by Hausner's factor values which were in the range of 1.16 to 1.32. Hence the prepared blends posses good flow property and can be used for manufacturing of the tablet. The values of angle of repose were found in the range of 20.22 to 24.61. The average weight of the Fast Dissolving tablet was 96.02 to 102.02 mg. Hardness of prepared tablet was between 3.02 to 3.45 kg/cm^2. The percent friability of formulations was found to be 0.55 to 0.65 and thus hardness

and friability of all formulation are found within the standard acceptable limit.

The disintegration time is very important and it is desired to be less than 1 minute. The quick disintegration may assist quick swallowing and drug absorption in buccal cavity, thus greater bioavailability of the drug. Disintegration time of prepared Fast Dissolving tablet was found in the range of 34 to 45 seconds. Swelling time is the indicator for the ease of disintegration of the tablet in the buccal cavity. It was observed that swelling time of tablet was in the range of 18 to 22 seconds. It was found that the nature of superdisintegrants present affected the swelling of the tablets. In Vitro dissolution study: In vitro dissolution study was performed by using Methanolic Sorenson's buffer pH 6.8 as dissolution medium using dissolution test apparatus LAB INDIA DS 8000 at a paddle speed of 50 rpm. At the end of 6 minutes the cumulative percentage drug release from various fast dissolving tablets was found in range 95.12% to 98.12%. This clearly indicates that when Superdisintegrants are used in combination than they provides better release than alone.

CONCLUSION:

It can be concluded from the whole study that Fast Dissolving tablets of Clinidipine drug. Natural superdisintegrant can be used as pharmaceutical excipients for oral drug delivery. So natural superdisintegrant like Isapghula Husk exhibited faster drug dissolution which leads to improve bioavailability, effective therapy (Therapeutic ratio), improve patient compliance, and satisfies all the standards as Fast Dissolving tablet. It was concluded formulation ST8 maximum percentage drug release was found 98.12, with Natural superdisintegrant 4%.

From the study, it was concluded that Isapghula Husk superdisintegrant showed better disintegrating property over the synthetic super disintegrate like, SSG(Sodium starch glycolate) CP (Crospovidone).

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