ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, Iss 11,Nov 2022

Formulation And Evaluation Of Felodipine Bilayered Tablet

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Abstract: Hypertension is a major risk for Cardiovascular and stroke complications. The good permeability and the poor water solubility (BCS class II) as well as short biological half-life characteristics of Felodipine selected as a drug candidate for bilayer preparations. Felodipine belongs to dihydropyridine derivative, which acts as a calcium channel blocker, used as an anti-hypertensive drug. Here the aim was to combine two Felodipine which are available in the market as single dose immediate release tablets. So the patients don't have to take two tablets. It will also reduce the cost of the tablet as immediate- release tablet or extended- release tablet.

Keywords: Hypertension, Felodipine, Bilayered tablet, Extended release, Immediate release

Introduction

Hypertension, commonly known as high blood pressure, is a medical condition in which the force of blood against the walls of the arteries is consistently too high. Blood pressure is measured in millimeters of mercury (mmHg) and is recorded as two values: systolic pressure (the pressure when the heart beats) and diastolic pressure (the pressure when the heart is at rest between beats) (Tripathi,KD., 1985).

Felodipine is a medication used to treat high blood pressure, also known as hypertension. It belongs to a class of drugs called calcium channel blockers. Felodipine works by relaxing and widening the blood vessels, which helps to lower blood pressure and reduce the workload on the heart(Ljung B., 1985).

Material and method

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Felodipine was obtained as a gift sample from JIJS chemical ltd., HPMC and MCC from SD Fine chemicals, PVP K30, Lactose, Talc, SSG and Magnessium stearate from Loba chemicals.

Precompression parametres

Bulk Density

25g of FDP powdered blend was weighed and transferred into 50ml measuring cylinders without tapping during transfer the volume occupied by powdered blend and granules was measured. Bulk density (Db) was calculated by following formula:

BD = m/Vo

Tapped density (Dt)

Where, m : Mass of the blend, Vo : Untapped Volume

Tapped Density

25g of FDP powdered blend was weighed and taken into graduated measuring cylinders. Initial volume occupied by drugs blends was noted down. Then cylinder was subjected to 500/ 750 and 1000 taps in tapped density tester (Electro Lab USPII) according to USP. Tapped density was calculated using the tapped volume and mass of powdered drugs using following formula:

TD = m/Vi

Where, m : Mass of the blend & Vi : Tapped Volume

Angle of repose

Flow property of the drugs was determined using Angle of repose method. The angle of repose of powdered drugs was determined by funnel method. A funnel was fixed at 2.5cm height on a burette stand and 25g powdered blend of FDP with excipients was passed through the funnel to form a pile. A circle was drawn across the pile to calculate the radius. Height of the pile was determined using two scale one vertical and one horizontal touching the tip of the pile. The same procedure was repeated for three times and the average value was taken. The angle of repose was calculated by using equation:

Tanq **= h / r**

Where, h and r are the height and radius of the granular cone. Result obtained after calculation was compared with the standard reading given in Table 6.9 to characterize the flow of the

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powdered drugs.

Compressibility Index

The Compressibility Index of the powder blend of FDP was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate atwhich it packed down. The formula for Carr's Index is as below

Carr′s index (%) =(Tapped density − poured density)/Tapped density *100

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is measurement of frictional resistance of the drug. It was determined by the ratio of tapped density and bulk density (Sinko Pj *et al*., 2006).

Hausner Ratio = Vo/Vi

Where, Vo: Tapped density, Vi: Untapped density

Formulation of the Fast-Release Layer of Felodipine

All ingredients were mixed well and triturated with FDP in a mortar with the help of pestle for 30min. Finally talc and magnesium stearate were added as glidant and lubricant, respectively, to the powder blend and mixed for an additional 5min. The resultant powder blend was compressed under constant pressure using a single punch tablet machine into 100mg tablets, each containing a total of 5mg FDP. Prepared tablets were evaluated for release pattern and best formula was selected for the final formulation of bi-layer tablets (Chrysant SG *et al*., 2003, Khan KA *et al*., 1972).

Formulation of the Extended-Release tablets of Felodipine

All ingredients were sifted through #30 sieves. FDP was accurately weighed (5mg per tablet) and was mixed with different ratios of MCC, HPMCK100, HPMCE5, Eudragit and lactose in a mortar with the help of pestle for 30min. The PVPK-30 binder solution was added slowly into this mixture. The wet mass was passed through sieve with 7mm screen. The wet mass was dried at 55-60°C and dried material was sifted through #20 sieves. Finally, magnesium stearate was added into the dried granules and mixed well. Granules were further compressed under a constant pressure using a single-punch tablet machine into 100mg tablets, each containing 5mg of FDP. Prepared tablets were evaluated for release pattern and best formula was selected for the final formulation of bi-layer tablets (Suresh KJN *et al*., 2018).

Formulation table of FDP from immediate release tablet

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Ingredients (mg)	Formulation code		
	F1	F2	F3
FDP	5	**5**	5
Crospovidone	5.0	-	-
Sodium starch glycolate	-	**5.0**	-
Croscarmellose sodium	-	-	5.0
Dicalcium phosphate	85	**85**	85
Magnesium stearate	2.0	**2.0**	2.0
Talc	3.0	**3.0**	3.0
Total Tablet weight	100	**100**	**100**

Formulation table of FDP from extended-release layer

Ingredients (mg)	Formulation code								
	E1	E2	E3	E4	E5	E6	E7	E8	E9
FDP	5	5	5	5	**5**	5	5	5	5
HPMCE5	5	7.5	10	-	-	-	-	-	-
HPMC K100M	-	-	-	5	**7.5**	10	-	-	-
Eudragit	-	-	-	-	-	-	5	7.5	10
Lactose	30	30	30	30	**30**	30	30	30	30
MCC	48	45.5	38	48	**45.5**	38	48	45.5	38
PVP K30	10	10	10	10	**10**	10	10	10	10
Magnesium stearate	2	2	2	2	**2**	2	2	2	2
Total weight	100	100	100	100	**100**	100	100	100	100

Evaluation Parameters

***In vitro* drug release profile:** The *in vitro* drug release study was carried out by using USP dissolution apparatus II (paddle type) (Bhardwaj V *et al*.,2010).

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Hardness

Tablet hardness testing, is the test to determine the breaking point and structural integrity of a tablet "under conditions of storage, transportation, and handling before usage". The breaking point of a tablet is based on its shape. Tablet requires a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the bi-layered tablet was determined using Monsanto hardness tester.

Weight variation test

All tablets, where the active ingredient comprises a major part of the tablet are required to meet a weight variation test. It is assumed that providing the weight of the tablet is kept within defined limits that the amount of active drug available to the user will remain the same. Twenty tablets were selected at random and the average weight was determined. Not more than two of the individual weights deviated from the average weight by more than limit

Friability (F)

Friability is the tendency for a tablet to chip, crumble or break following compression. This tendency is normally confined to uncoated tablets and surfaces during handling or subsequent storage. Friability is the loss in weight of tablet in the container due to removal of fine particle from their surface. The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (%). 20 tablets were initially weighed (initial weight) and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 mins. The tablets were weighed again (final weight). The % friability was then calculated by the following formula:

F=(Initial Weight – Final weight) / Initial weight *100

Thickness

The weight of a compressed tablet is dependent on diameter and thickness of the tablet. In theory, the thickness of the tablets was measured using Digital Vernier Caliper. It is expressed in mm.

Percentage Drug Content

Bi-layer tablet was powdered and dissolved in PBS pH 7.4. After suitable dilutions the solution was analyzed in UV-spectrophotometer at 360nm using PBS pH 7.4 as blank.

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In vitro dissolution studies

Dissolution rate studies of Bi-layer tablets were performed in PBS pH 7.4. This test was performed using the USP dissolution apparatus type II at 50 rpm. Bi-layer tablet was placed in the dissolution vessel containing 900mL of PBS pH 7.4 maintained at 37±0.5^{0}C. At pre-decided intervals, samples from the dissolution medium were withdrawn, filtered, and concentrations of FDP were determined spectrophotometrically at λ_{max} 360 nm. FDP release from final formulation was determined by plotting concentrations of FDP on calibration curve.

Stability Studies

Stability is one of the crucial studies to be performed during the development and designing of the delivery system. Bi-layer tablets were assessed for their stability with respect to the any change in drug content. The studies were conducted as per ICH guidelines which recommends a temperature of 40±2^{0}C, a relative humidity of 75±5% and period of 3 months for accelerated stability studies. However, the stability was also assessed at 4±1^{0}C (refrigerated condition) and at 25±2^{0}C with 60±5% relative humidity. The sampling time was kept at 1, 2 and 3 months (Siddique S *et al*., 2008, Vidyadhara S *et al*., 2006, Rama B *et al*., 2014).

RESULTS AND DISCUSSION

In vitro release profile of FDP from immediate release tablet

Time(min)	Cumulative % drug release		
	F1	F2	F3
15	34.25	**35.82**	33.38
30	58.74	**62.58**	59.27
45	80.57	**89.43**	81.29
60	98.06	**99.47**	98.91

In vitro release profile of FDP from extended-release tablets

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Time (hrs)	Cumulative % drug release								
	E1	E2	E3	E4	E5	E6	E7	E8	E9
0.5	4.68	4.23	5.27	4.74	**3.46**	3.15	3.35	3.58	2.95
1	9.24	8.57	7.63	7.58	**7.12**	8.29	7.91	7.61	6.88
2	19.30	19.12	21.89	18.53	**18.38**	19.24	18.97	17.12	16.70
4	31.82	32.59	31.43	30.68	**29.54**	36.67	33.25	33.05	31.68
6	45.64	45.36	48.48	42.80	**42.63**	45.45	44.17	44.08	43.39
12	94.22	91.85	90.57	88.29	**88.17**	94.45	92.38	92.15	91.86

Evaluation of FDP Bi-layer tablets

Parameter	Unit	F2E5
Thickness	Mm	3.28
Hardness	Kg/cm^2	6.8
Friability	%	0.38
Weight Variation	%	1.28

***In vitro* release profile of FDP from Bi-layer tablets**

Time (hrs)	Cumulative % drug release
0.25	5.86±1.2
0.5	10.54±1.6
1	22..32±3.2
2	38.44±2.1
4	56.15±4.8

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6	68.94±3.6
12	78.61±2.2

Value represents mean ± SD (n=3)

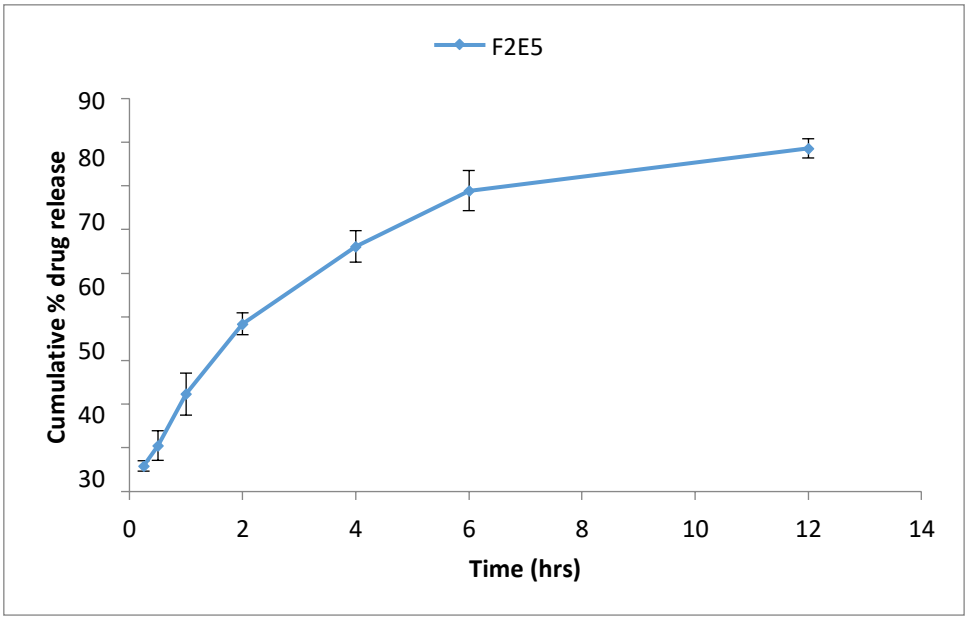

Fig 1 *In vitro* release profile of FDP from Bi-layer tablets

Stability studies at different conditions (F2E5)

Storage Conditions	Formulation (F3)	Observations on storage for Drug content (%)			
		Initial	1 month	2 months	3 months
4±1°C	% Drug Content	100%	100%	99.82±0.41%	99.61±0.34%
	Appearance	White	No change	No change	No change
25±2°C and 60±5% RH	% Drug Content	100%	100%	99.73±1.6	99.54±1.3%
	Appearance	White	No change	No change	No change
40±2°C and 75±5% RH	% Drug Content	100%	99.65±2.7	99.38±3.1	99.14±1.6%
	Appearance	White	No change	No change	No change

Values are mean± SD (n=3)

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CONCLUSION

Bi-layer tablet is the beneficial technology when compared to single layer tablet. By this technique even the incompatible drugs can be compressed into a single tablet. Bi-layer tablet helps in sequential release of drug in which one as the immediate release and the other as the controlled release. The present work involves the formulation development, optimization and in-vitro evaluation of bi-layer matrix tablets of felodipine.

The final suitable formulation was achieved fruitfully with the combination of Polymers that is MCC and HPMC K100M produced desired release profile for felodipine extended-release layer. The combination of disintegrating agents (Sodium starch glycolate) and Dicalcium phosphate produced desired release rate for immediate release layer. The results reveal that formulation F2E5 has met the objective of extended drug release for over a period of 12 hrs. Since the Bi-layer tablet has shown to be efficacious with good release profile, this Bi-layer tablet can be used in the management of mild to moderate hypertension.

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