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Design, development and optimization of Amlodipine Besylate tablets

Margaret Chandira*[1], A. Pasupathi[1], P. Elamathi[1], Debjit Bhowmik[1], Chiranjib[1], Pankaj[1], B. Jayakar[1], K. P. Sampath Kumar[2]

[1]*Vinayaka Missions College of Pharmacy,Vinayaka Mission University, Salem*
[2]*Department of Pharmaceutical Sciences, Coimbatore Medical College, Coimbatore, Tamilnadu*

Abstract

The objective of the present study was to develop a tablet formulation of amlodipine besylate calcium channel blocker for better management of hypertension and also suitable in the treatment diabetic hypertension patients, In the present study amlodipine besylate 10 mg tablets have been formulated and developed using direct compression techniques, to provide a safe, highly effective method for treating severe hypertension while reducing undesirable adverse effects. Preformulation parameters were studied for the formulated batches. Amlodipine besylate had maximum solubility in PH3 and thus most suitable medium for amlodipine besylate dissolution studies .the dissolution profile of the formulated formulation was compared with the marketed preparation. The results indicated improved dissolution profile of formulation no. F10 take 30 minutes for complete drug release. To develop 10 mg tablet dosage form for amlodipine besylate using market sample as a reference product strategy with reduced average weight compared to innovator product. To provide the patient with the most conventional mode of administration, there was need to develop of Amlodipine besylate tablet.

Keywords: Tablet, dissolution, direct compression, hypertension, disintegration time.

Introduction

Tablet product design requires two major activities. First, formulation activities begin by identifying the excipients most suited for a prototype formulation of the drug. Second, the levels of those excipients in the prototype formula must be optimally selected to satisfy all process/product quality constraints. Tablets may be defined as solid pharmaceutical dosage forms containing drug substance with (or) without suitable diluents and prepared by either compression (or) moulding. Amlodipine besylate is a dihydro pyridine calcium antagonist (calcium ion antagonist or slow channel blocker) that inhibits the trans membrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Amlodipine besylate is a second

generation of dihydropyridine-3,5-dicarboxylate derivative of long acting calcium channel blockers. That differs from other calcium channel blockers because of its unique pharmacokinetic profile and has wide scope of clinical applications. Experimental data suggest that amlodipine besylate binds to both dihydro pyridine and non dihydro pyridine binding sites. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extra cellular calcium ion influx across cell membranes selectively, with a greater effect on vascular smooth muscle cells than on cardiac muscle cells. Objectve of present study was to develop such as novel drug delivery system for Amlodipine besylate by simple and cost effective direct compression method.

Materials and Methods

Amlodipine besylate is procured by Cadila health care Ltd ,Ahmedabad, Starch, Di-calcium phosphate are gifted by Maple biotech,pune, Microcrystalline Cellulose, Sodium starch glycolate are gifted by Signet Chemicals corporation, Mumbai, Magnesium Stearate, Isopropyl alcohol are procured by Loba chemie,Cochin.

Formulation of amlodipine besylate tablets

Amlodipine besylate tablets can be prepared by using direct compression technique amlodipine besylate directly compressible and diluents like microcrystalline cellulose (MCC PH 102), dibasic calcium phosphate disintegrating agent like sodium starch glycolate was added and starch were mixed .The final powder was Lubricated with magnesium stearate and compressed as described earlier.The active ingredient was weighed and passed (sieve) through mesh no.40 and starch, microcrystalline cellulose and dibasic calcium phosphate, sodium starch glycolate were passed (sieve) through mesh no 60.the active ingredient, microcrystalline cellulose dibasic calcium phosphate, sodium starch glycolate were mixed in a poly bag for 5 minutes. Starch blend, magnesium stearate were weighted and passed through mesh no.60. Above, all the ingredients were mixed well in a poly bag for 3 minutes. Then the granules were compressed with embossing A/10 upper punch. Lower punch size “U” 10/32 FB (Flat Beveled) round shaped punches.

Wet Granulation Technique

Table 1: Formulation of the Batch no: - (F1 To F2)

Sl. No.	Composition	Formulation	
		F 1Qnty/tab (mg)	F 2Qnty/tab (mg)
1.	Amlodipine Besylate	13.87	13.87
2.	Microcrystalline Cellulose pH 102	112.0	112.0
3.	Dibasic Calcium Phosphate	62.13	62.13
4.	Sodium starch Glycolate	8.0	8.0
5.	Starch	2.0	2.0
6.	Magnesium stearate	2.0	2.0
7.	Isopropyl alcohol	15ml	-
8.	Water	-	25ml
	Total	**200**	**200**

Direct Compression Technique

Table 2: Formulation of the Batch No: (F3 To F10)

Sl. No.	Composition	Formulation							
		F3 Qnty/ tab (mg)	F4 Qnty/ tab (mg)	F5 Qnty/ tab (mg)	F6 Qnty/ tab (mg)	F7 Qnty/ tab (mg)	F8 Qnty/ tab (mg)	F9 Qnty/ tab (mg)	F10Q nty/ta b (mg)
1.	Amlodipine Besylate	13.87	13.87	13.87	13.87	13.87	13.87	13.87	13.87
2.	Microcrystalline Cellulose pH 102	100.0	100.0	100.0	105.0	106.0	115.0	114.0	113.0
3.	Dibasic Calcium Phosphate	75.13	77.13	79.13	76.13	75.13	67.13	64.13	62.13
4.	Sodium starch Glycolate	8.0	6.0	4.0	2.0	2.0	1.0	1.0	1.0
5.	Starch	2.0	2.0	2.0	2.0	2.0	2.0	6.0	8.0
6.	Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	2.0
	Total	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

Preformulation Study

In the preformulation study Amolodipine besylate was characterized for organoleptic properties, solubility, bulk density, tapped density, angle of repose . Results of the compressibility index, Hauser's ratio and angle of repose show that the all material has sufficient compressibility and flow properties.

Result of Organoleptic properties by bulk and tapped density

Table 3 : Results of organoleptic properties

Properties	Results
Description	Crystalline
Solubility	Slightly soluble in water
Taste	Slightly bitter
Odor	Odorless
Colour	Off white
Melting Point	195°C – 204°C

Table 4 : Results of Bulk and Tapped Density

Properties	Results
Loss on Drying (%w/w)	0.35
Bulk Density (gm/cm^2)	1.11
Tapped Density (gm/cm^2)	7.40
Compressibility Index	85
Hauser's Ratio	6.67

Evaluation of Powder Blend

a. Bulk density and tapped density
Bulk density and tapped density of powder blend was evaluated. The results were shown in the Table No.5.

b. Angle of Repose
The angle of repose for the entire formulations blend was evaluated. The results were shown in the Table No. 5.

c. Compressibility Index
Compressibility index for the entire formulations blend was evaluated. The results were shown in the Table No. 5

d. Hausner`s Ratio
The Hausner`s ratio for the entire formulations blend was evaluated. The results were shown in the Table No.5

Table 5 : Granules Parameters Trials Reported From (F1 to F10)

Sl. No.	PARAMETERS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Bulk Density (gm/ml)	0.42	0.42	0.43	0.43	0.42	0.44	0.42	0.46	0.46	0.42
2.	Tapped Density (gm/ml)	0.54	0.56	0.59	0.59	0.53	0.54	0.53	0.55	0.54	0.53
3.	Compressibility index (%)	22.02	25.09	28.06	28.12	19.02	18.32	19.04	16.32	14.05	18.01
4.	Haunser ratio	1.28	1.33	1.37	1.37	1.37	1.20	1.28	1.19	1.17	1.26
5.	Angle of repose (θ^0)	28.30	28.17	26.56	27.43	29.64	28.43	28.56	23.92	23.96	26.23

Physical Parameter

Weight Variation
All the formulation tablets were passed weight variation test as the % weight variation was within the USP limits of ± 5.0% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values. The prepared formulation complies with the weight variation test.

Thickness
The maximum thickness of the formulation was found to be 3.1mm. The minimum thickness of the formulation was found to be 2.8 mm. The average thickness of the all formulation was found to be 2.9 mm.

Hardness

The maximum hardness of the formulation F5 was found to be 6 Kg/cm^2 . The minimum hardness of the formulation F3 was found to be 3 Kg/cm^2 The hardness of best formulation F10 was found to be 4 Kg/cm^2.

Friability Test

The maximum friability of the formulation was found to be 0.18%. The minimum friability of the formulation was found to be 0.11 %. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

***In-vitro* Disintegration Test**

In-vitro disintegration time Amolodipine Besylate Tablet was found to be in the range of 12 min. and innovator disintegration time was found to be 13 min.

Table No. 6 : Compression Parameters Trial Report from (F1 to F10)

	PARAMETERS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Hardness (Kg/cm^2	4-5	4-5	5-6	5-6	5-6	4-5	4-5	3-5	3-5	4-5
2.	Thickness (mm)	2.7-3.1	2.7-2.9	2.6-2.7	2.5-2.6	2.5-2.6	2.8-2.9	2.8-3.2	2.8-3.1	2.8-3.1	2.8-3.1
3.	Friability (%)	0.14	0.12	0.15	0.18	0.15	0.13	0.12	0.18	0.15	**0.11**
4.	Disintegration test (min.)	12	14	15	14	11	14	13	12	14	**12**

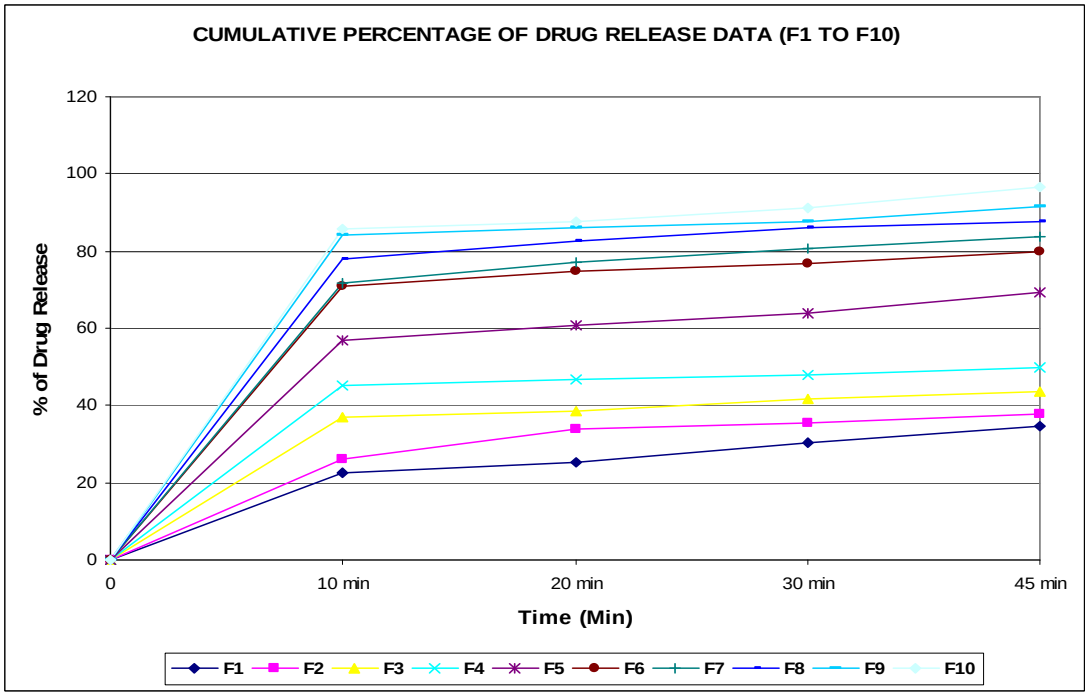

Fig. No. 1 : Cumulative Percentage of Drug Release Data from (F1 to F10)

The results are showed in the above figure depicting all the formulation from (F1 to F10).

Table No.7 : Cumulative Percentage of Drug Release of Innovator Product

formulation	Tablets	10 min(%)	20 min (%)	30 min(%)	45 min (%)
INNOVATOR	1	80.79	86.65	89.45	89.13
	2	90.72	86.76	89.78	90.62
	3	83.61	87.34	89.56	90.98
	4	85.59	87.65	89.62	92 .40
	5	90.23	88.02	90.13	94.78
	6.	89.75	88.69	90 .61	95.80
	Mean	86.78	87.57	89.85	93.05

This formulation showed that the each tablet released drug more than 86.78 %in 10 min and in 45 min average release of the drug 93.05%. In-vitro dissolution study was carried out for formulation No. F10 and compared with innovator product formulation No. F10 has taken 30 minutes for complete drug release while innovator product has taken 45 minutes, more than drug release.

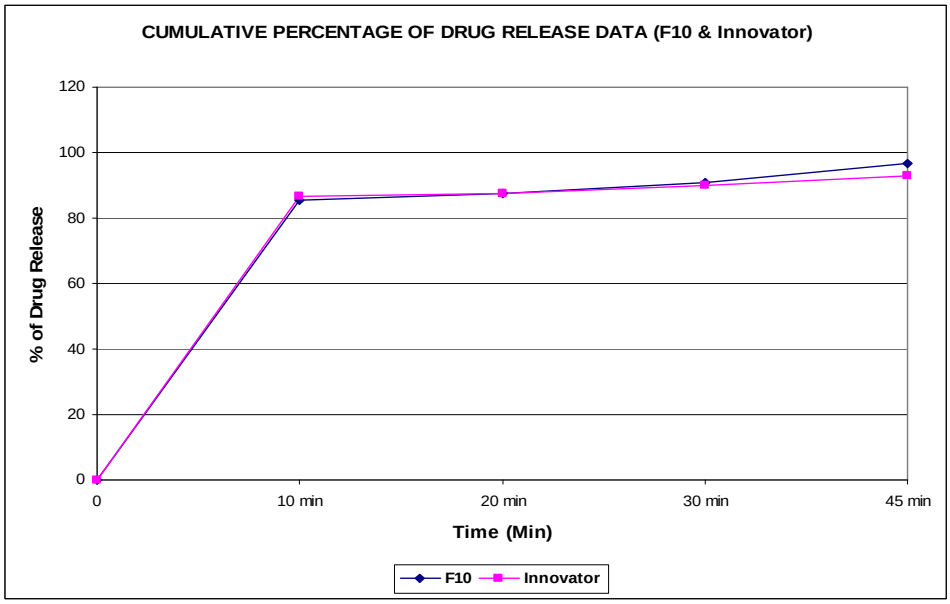

Fig. No. 2: Cumulative Percentage of Drug Release Data F10 & Innovator

In vitro dissolution study was carried out for formulation No. F10 compared with innovator product (drug as such) formulation to have taken 30 minutes for complete drug release. While innovator product has taken 45 minutes for complete drug released.

Table No.8 : Comparative Evaluation Study Reports

Sl.No	Brand Names	Average Weight of 20 Tablets	Thickness (mm)	Hardness (Kg/cm^2)	Disintegration time (min)	Friability (%)
1.	F10	4.003	3.1	4.5	12 sec	0.11
2.	INNOVATOR PRODUCT	4.005	4.1	5.6	13 sec	0.12

Assay by HPLC

Column	:	Phenomenex x 250 x 4.6mm, 5µ C18
Wave Length	:	237nm
Flow Rate	:	1.0ml/minute
Injection Volume	:	10µl
Mobile Phase	:	Buffer : Acetonitrile : methanol (50 : 15 : 35)

This method was found to be accurate, precise and specific for Amlodipine Besylate. The result were shown in the Table No. 25 and in figure No .20, 21.

Table No. 9 Percentage of Drug Content

SL.NO	FORMULATIONS F1 –F10	% DRUG CONTENT
1.	F1	65.81
2.	F2	69.71
3.	F3	71.85
4.	F4	73.96
5.	F5	76.02
6.	F6	81.38
7.	F7	85.69
8.	F8	89.93
9.	F9	98.46
10.	F10	99.96

Table No. 10 : Optimized Formulation – (F10)

Sl. No.	Composition	F10 Qnty/tab (mg)
1.	Amlodipine Besylate	13.87
2.	Micro crystalline Cellulose pH 102	113.0
3.	Dibasic Calcium Phosphate	62.13
4.	Sodium starch Glycolate	1.0
5.	Starch	8.0
6.	Magnesium stearate	1.0
	Total	**200**

FOURRTS INDIA LABORATORIES Pvt.LIMITED

SAMPLE NAME:AMLODIPINE BESYLATE
ACQ.OPRATIOR:P.ELAMATHI
ACQ.METHOD:
INJECTION DATE:11-10-2008
DATA FILE:C:\HPCHEM\1\DATA\2008\OCT-08\AMLODIPINNE BESYLATE-1006.D

INSTRUMENT CODE 1/QC/HBC/02
SEQ LINE: 3.000
LOCATION: VIAL3
INJECTION TIME:03:47:06PM

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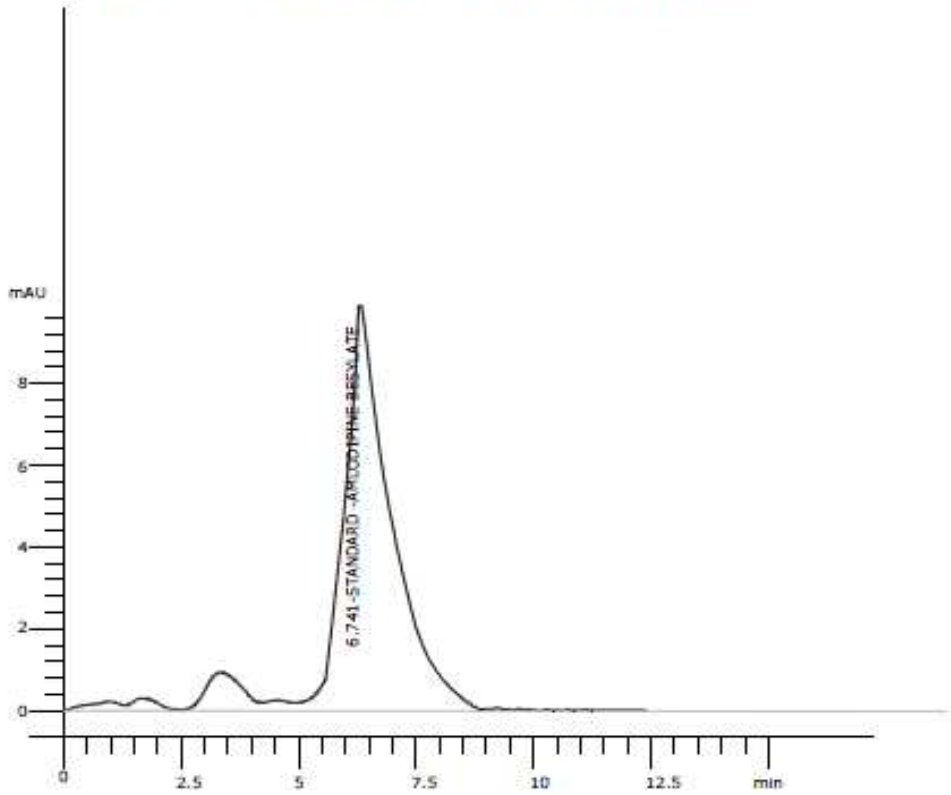

Customized report:PRODUCT

PEA #	NAME	RT [MIN]	AREA	AREA%
1	STANDARD- AMLODIPINE BESILATE	6.74	652.986	100.000

FOURRTS INDIA LABORATORIES Pvt.LIMITED

SAMPLE NAME:AMLODIPINE BESYLATE
ACQ.OPRATIOR:P.ELAMATHI
ACQ.METHOD:
INJECTION DATE:11-10-2008
DATA FILE:C:\HPCHEM\1\DATA\2008\OCT-08\AMLODIPINNE BESYLATE 1006.D

INSTRUMENT CODE 1/QC/HBC/02
SEQ LINE: 3.000
LOCATION: VIAL3
INJECTION TIME:04:17:06PM

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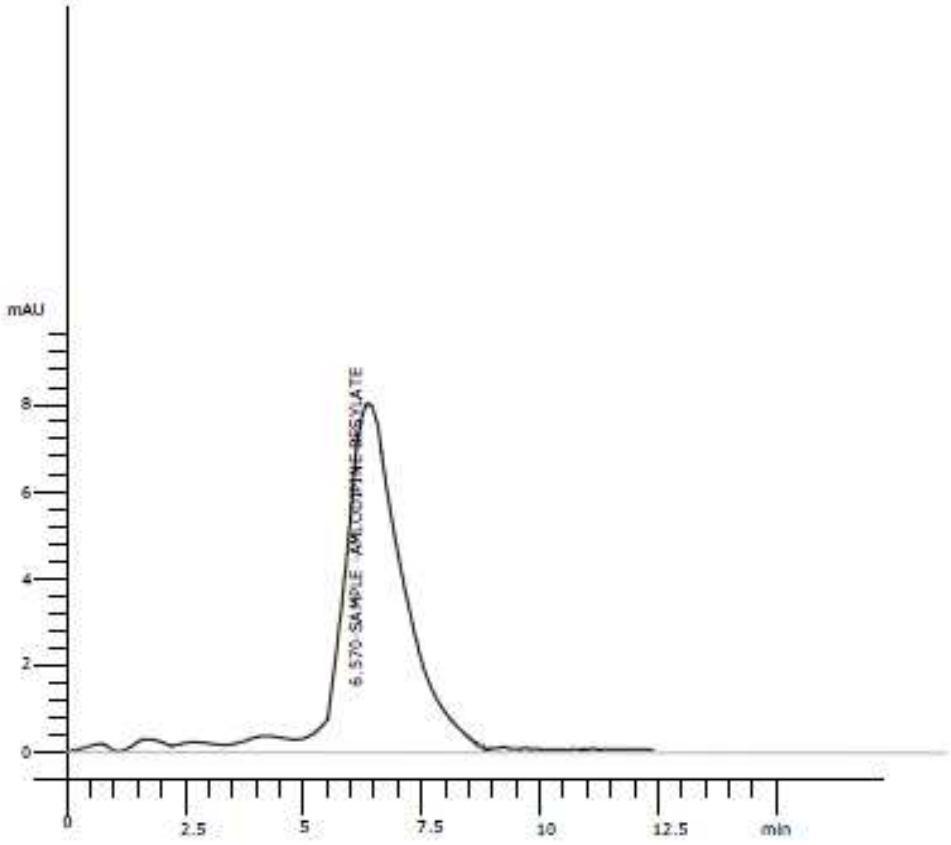

Customized report:PRODUCT

PEA #	NAME	RT [MIN]	AREA	AREA%
1	STANDARD AMLODIPINE BESILATE	6.57	652.759	100.000

Stability Testing

Table No.11: Results of the Physical Observation of Optimized Formulation (F10)

Batch No.	Initial	40^0C / 75% RH			
		1st Week	2nd Week	3rd Week	4th Week
A	Off-White	+	+	+	+
B	Off-White	+	+	+	+
C	Off-White	+	+	+	+
D	Off-White	+	+	+	+
E	Off-White	+	+	+	+

Stability study was carried out for the optimized batch formulation according to ICH guide lines at 40^0C/75%RH for one month.

The result showed that there was no significant change in physical and chemical parameter of the tablet, hence the optimized formulation formulation No. (F 10) was found to be stable.

Table 12 : Stability Testing of Optimized Formulation (F10)

Storage Conditions	Months	Description	Disintegration test (min)	Assay (%)
(40° C ± 2°C, 75% RH).	1st	White colour round shaped Tablets	23	98.63
	2nd		26	97.38
	3rd		28	96.41

Table No.13 Stability Study of In-Vitro Dissolution for Optimized Formulation(F10)

Time (min)	Cumulative % drug Release		
	Room Temp.	25^{cz}/60% RH	40-75% RH
0	**0**	**0**	**0**
10	**81.56**	**79.09**	**75.1**
20	**98.28**	**97.27**	**81.73**
30	**101.68**	**98.18**	**88.69**
45	**102.75**	**99.81**	**87.34**

Stability study was carried out for the optimized batch formulation No. F10 according to ICH guide lines at 40^0C/75%RH for 3 months.

The stability study results revealed that the optimized formulation F10 was found to be stable. From the above stability reports we can conclude that the formulation No. F10 was said to be stable.

Conclusion

The project work entitled, Formulation development, and optimization of amlodipine besylate tablet 10 mg was carried out in the present study it was mainly concentrated on the optimization of the formulation to meet the USP requirements mainly dissolution parameter. The Optimized formulation F10 was studied for the drug content and in-vitro drug release. It was compared with the available marketed formulation. Tablet blends were evaluated for various parameters such as bulk density, tapped density, and tablets were evaluated for thickness, drug content, hardness, and weight variation. It was revealed that the tablets of all batches had acceptable physical parameters. In the present study amlodipine besylate 10 mg tablets have been formulated and developed using direct compression technique, to provide a safe, highly effective method for treating severe hypertension while reducing undesirable adverse effects. Pre and post formulation parameters were studied for the formulated batches. Amlodipine besylate had maximum solubility in pH3 and thus most suitable medium for amlodipine besylate dissolution studies .the dissolution profile of the formulated formulation was compared with the marketed formulation. The results indicated improved dissolution profile of formulation F10 .The result of all the physical and in-vitro dissolution data concluded that formulation F10 was the most promising formulation when compared to innovator product. The formulation and evaluation of formulation (F10) was encouraging. The trial conducted with the consecutive three batches revealed relative standard deviation below 4 %, indicative the insignificant batch-to-batch variation. The formulation showed improved dissolution as compared to the marketed preparation. Amlodipine besylate using microcrystalline cellulose: Starch blend would be cost effective and dissolution mediums pH 3 would the ideal media for conducting dissolution studies. Stability study Stability study was carried out for the optimized formulation according to ICH guide lines at 2–8° C (controlled sample), Room temperature and 40° C / 75%RH for 1 month. Tablets were evaluated for assay Disintegrating time, in-vitro drug release profile after one month. The results showed that there was no significant change in physical and chemical parameter of the tablet, hence the formulation was found to be stable. It concluded that Formulation F10 was stable.

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