Formulation and Evaluation of Orodispersible tablets of Nifedipine 10 mg.

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Abstract

The most common preferred route is oral rout of administration. Today oro-dispersible tablet from novel drug delivery system gain importance from patient. Which is administer to the patient to control the attack of angina or hypertension, but for immediate control, Oro-dispersible tablet is oral solid dosage form in which the tablet gets dispersed in oral cavity in absence of water. Various manufacture are formulated this formulation by various method. The most importance thing in this formulation are masking of taste of drugs. Generally oro-dispersible tablet are prepared by direct compression method. Dry granulation, wet granulation, Spry drying is the various methods for preparation of oro-dispersible tablet. Oro-dispersible tablet generally contains filler, glidant, anti-adherent super disintegrate, sweetener and resins. Evaluation parameter includes hardness, friability, wetting time, moisture uptake, disintegration test, and dissolution test. Wetting time, Disintegration time, and Dissolution test is directly proportional to the hydrophobic ingredient added for lubrication, anti-adherent, Glidant action. These hydrophobic ingredient are Magnesium Stearate. To oppose the action of magnesium stearate, hydrophilic additives are incorporated viz Sodium lauryl sulphate

Keywords: Oro-dispersible tablet, wetting time, Dissolution test

1. INTRODUCTION

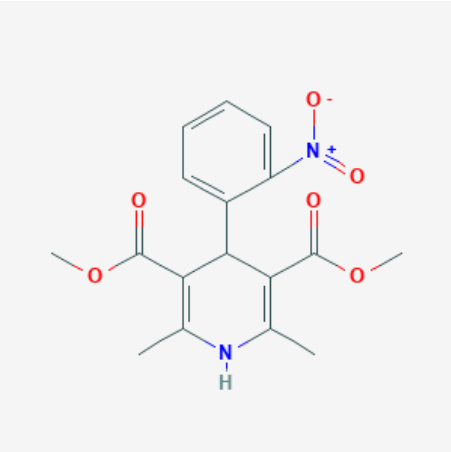
Quality are built in the pharmaceutical formulation by design the formulation. The total quality in the product are known as Total Quality Management. To gain this goal of optimized quality product, the knowledge obtained from pharmaceutical development studies and manufacturing provides the scientific background. Although it is based on different pharmaceutical studies, but it has its aim that it minimizes the end product testing and Increases the chances of regulatory acceptance by different pharmaceutical governing bodies. The aim and objective of the present study is to develop and evaluate oro dispersible tablet of Nifedipine and enhance the onset of action of Nifedipine and also to study the influence of excipients on the physical characteristics of the tablets by applying two level three factor factorial designs taking Nifedipine as model drug which is used in the treatment of the Hypertension, Angina Pectoris, cardiac arrhythmia. The study of this formulation to select the best possible excipient combination of semi synthetic & natural and artificial additives to development of formulation. Super disintegrants viz Cross carmillose sodium are added to formulate the dispersible tablets among all the diluents and disintegrants used. Finally the effect of the additives or various excipients ratio and super disintegrants on various properties of the tablet were also determined.

2. MATERIAL AND METHOD

2.1 API Structure Characterization:

Formula	: $C_{17}H_{18}N_2O_6$
Molar mass	: 345.335 g / mol
Melting point	: 172 to 174 ºC

Nifedipine was patented in 1967 and approved for use in the United States of America in 1981. It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system for various cardiac diseases. It is available as a generic medication in various dosage form and various formulation range from 5 mg to 20 mg. Nifedipine is odorless, yellow crystalline tasteless Powder. Nifedipine is water insoluble. Chemically Nifedipine is a Dihydropyridine Calcium Channel Blocker. The mechanism of action of Nifedipine on heart is as a Calcium Channel Antagonist. The chemical classification of Nifedipine is Dihydropyridine. Nifedipine is a first generation calcium channel blocker used to treat hypertension and angina pectoris and other cardiovascular diseases. Nifedipine therapy is associated with a low rate of serum enzyme elevations and has been linked to several instances of clinically apparent acute liver injury. Nifedipine is a potent vasodilator agent with calcium antagonistic action. It is a useful anti-anginal agent that also lowers blood pressure and hypertension.



IUPAC Name
Dimethyl 2, 6-dimethyl-4-(2-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate.

2.2 Pre formulation Studies:

Drug Solubility: As per the research study from the Nifedipine Wikipedia the Solubility of the drug at 20° C (g/L): acetone 250, methylene chloride 160, chloroform 140, ethyl acetate 50, methanol 26, ethanol 17. But practically we found the solubility of Nifedipine was checked in different solvents which are shown in following table.

Sr. No.	Solvents	Mg/ ml
1	Water	0.001
2	Ethanol	12.5
3	Chloroform	76.25
4	Acetone	295.5
5	Hydrochloric acid 0.1 N	0.025

2.3 Drug and Excipients studies:

S. No.	Drug+ Excipients	Duration (months)	Result
1	Drug+ Starch	6 Months	Stable
2	Drug+ Talcum	6 Months	Stable
3	Drug+ Mag. Stearate	6 Months	Stable
4	Drug +MCCP	6 Months	Stable
5	Drug +Lactose	6 Months	Stable
6	Drug +CCS	6 Months	Stable
7	Drug +Saccharine	6 Months	Stable
8	Drug +DC starch	6 Months	Stable
9	Drug+ SSG	6 Months	Stable
10	Drug+ Mannitol	6 Months	Stable

2.4 MTERIAL AND THEIR USE WITH OBTAINED SOURCE

Sr. No.	Material	Uses of Ingredients	Sources
1	Nifedipine	Active Ingredients	J.B. Chemicals Ankleshwer. Bhruch.
2	Starch DC Grade	Diluents	Pacific India. A farmaceutical Exporter, Villalge: Dhana, Baghbania. Nalagarh. Solan.
3	Lactose	Diluents	
4	Cross Carmillose Sod.	Super disintegrants	
5	Talcum	Lubricants	
6	Magnesium Stearate	Glidant	
7	Starch	Antiadhrants	

8	Sodium Saccharine	Sweetener	Himachal Pardesh
9	Micro crystalline cellulose	filler	

2.5 Preparation of Nifedipine 10 mg tablet by direct compression method.

Formulation table.

Serial No.	Ingredients	C1 (mg)	C2 (mg)	C3 (mg)	C4 (mg)	C5 (mg)
1	Nifedipine	10	10	10	10	10
2	Starch DC	60	60	60	60	60
3	Lactose	70	65	60	55	50
4	Mannitol	15	15	15	15	15
5	Aspartame	2.5	2.5	2.5	2.5	2.5
6	Talcum	7.5	7.5	7.5	7.5	7.5
7	Mag. Stearate	5	5	5	5	5
8	Sodium CMS	-	5	10	15	20
9	SSG	10	10	10	10	10
10	Total weight (mg)	180	180	180	180	180

All the ingredients viz active ingredients, additives were passed through 60 # sieve separately, Magnesium stearate & Talc through 40 #. Then the ingredients were weighed and mixed in double dilution order or Geometric mixing and tablets were compressed with 7 mm sizes biconvex round punch to get tablet using Rimek double rotary Compression Machine.

3. Post compression Parameters:

3.1 Thickness of compressed tablet.

The thickness of the compress tablets of Nifedipine was determined using a Digital Vernier calliper. Ten tablets from each type of formulation were used and average values were calculated. It is expressed in mm.

3.2 Hardness

The resistance of tablets during passing through hopper, Blister Cartooning, breakage, under conditions of storage, transportation and Handling before usage are directly proportional to its hardness. For each formulation, the hardness of 6 tablets was determined using the Pfizer Hardener Tester and Monsanto hardness tester. The tablet was held along its oblong axis in Between the two jaws of the tester. At this point, reading should be zero kg/cm2. Then constant force was applied by rotating the knob in Monsanto tester and in case of Pfizer directly force applied until the tablet breakdown in the pieces. The reading the both cases at this point was noted.

3.3 Friability Test:

Friability Test is generally used the measure of tablet strength. Roche Friability tester was used for testing the friability using. In This test subjects a number of compressed tablets to the combined effect of shock abrasion by utilizing a circular plastic chamber which revolves at a speed of 25 revolution per minutes for 4 minutes i.e. 100 rpm, dropping the compressed tablets of Nifedipine to a distance of 6 inches in each revolution. A sample of weighed 6 compressed tablets of was placed in Roche friability chamber which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then de-dusted, and broken tablet are removed and reweighed. A loss of less than 1 % in weight in generally considered acceptable according to Pharmacopeia. Percentage friability (% F) was calculated as follows:

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

3.4 Weight variation test:

As per the limitation of Pharmacopeia to find out weight variation test, 20 tablets of each type of formulation were weighed individually using single pan balance or an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.

Specifications for tablets as per Indian Pharmacopeia. 1996.

S. No.	Percentage Deviation	Average Weight of Tablet (mg)
1	10	80 mg or less
2	7.5	More than 80 mg but less that 250 mg
3	5	250 or more

3.5. Uniformity of drug content:

Five tablets of each compression formulation are weighed and crushed in mortar Pastel and powder, or crushed equivalent to 10 mg of Nifedipine was weighed and dissolved in 100 ml of 0.1N Hydrochloric acid (pH 1.2). This was the stock solution from which 0.2 ml sample was withdrawn and diluted to 10 ml with 0.1N Hydrochloric acid. The absorbance was measured at wavelength 237.5 nm using double beam Ultra Violet Visible spectro photometer. Content uniformity of the drug was calculated using formula.
% Purity of the Drug = 10 C (Au / As) -------
Where, C = Concentration,
Au and As=Absorbance's obtained from unknown preparation and standard Preparation.

3.6. Wetting time:

This method is applied to calculate tablet wetting time. A piece of tissue paper or absorbent folded twice was placed in a small Glass Petri dish having the diameter 6.5 cm, containing 10 ml of water. Compressed tablet was placed on the paper, and the time record or note for complete wetting. Three trials for each batch were performed and standard deviation are calculated.

3.7. In vitro disintegration time:

The process of breakdown or convert the tablet into pieces or into smaller particles is called as disintegration. The in vitro Disintegration time of a tablet was determined using disintegration test apparatus as per Indian Pharmacopeia specifications. Place one tablet in each of the 6 tubes of the basket. Add a disc to each tube and run the apparatus using distilled water maintained at 37° ± 2°C which is similar to body temperature. The assembly should be raised and lowered between 30 cycles per minute in the 0.1 N HCL or Distilled water maintained at 37° ± 2°C. The time in seconds taken for complete disintegration of the tablet.
In this disintegration test if the tablet are adhere to the 10 # sieve then continue the test till all tablet are completely disintegrated.

3.8. In vitro dissolution test:

Rate of dissolution are studied by using USP type-II apparatus having 50 rpm, using 900ml of 0.1 N Hydrochloric acid as dissolution solvent. Temperature of the dissolution medium was maintained at 37 ± 0.5°C. The sample of dissolution medium was withdrawn at every 5 min interval and first filtered. The absorbance of filtered solution was measured by using Ultra Violet spectrophotometric method at 237.5 nm and concentration of the drug was determined from standard calibration curve.
In vitro drug release studies details:

- ✓ Dissolution test apparatus
- ✓ 0.1 N HCL as Dissolution medium
- ✓ 900 ml Dissolution medium volume
- ✓ 37 ± 0.5°C as std. Temperature
- ✓ 50 rpm Speed of basket paddle
- ✓ 5 min sampling intervals
- ✓ 10 ml volume Sample withdraw
- ✓ 237.5 nm Absorbance measured

4. Result and discussion:

4.1 Pre compression Parameter and studies

S. No.	Formulation code	Angle of Repose	Bulk density (weight/ml)	Taped Density (weight/ml)
1	C1	27.92±0.70	0.41±0.02	0.49±0.04
2	C2	26.10±0.56	0.42±0.03	0.48±0.02
3	C3	25.86±0.63	0.42±0.03	0.49±0.04
4	C4	25.14±0.45	0.41±0.02	0.48±0.02
5	C5	24.40±0.69	0.42±0.03	0.48±0.02

4.2 Post compression Parameter Studies.

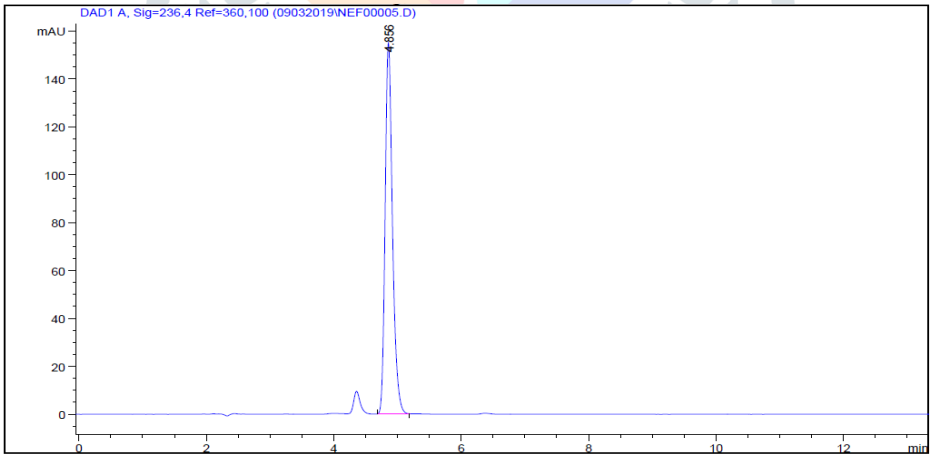
Formulation code	Hardness (KG/cm2)	Friability (%)	Thickness (mm)	Diameter (mm)	Weight (mg)
C1	4.20	0.85	3.55	7.02	192
C2	3.80	0.74	3.52	7.04	185
C3	3.20	0.66	3.49	7.00	178
C4	3.70	0.45	3.48	7.02	176
C5	3.50	0.32	3.54	7.01	181

4.3 Post compression studies:

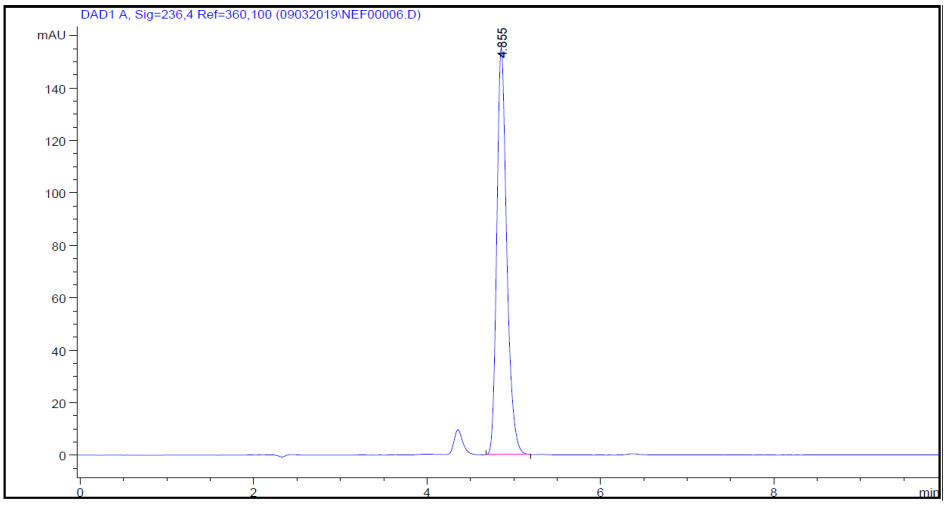
Formulation code	Assay of Drugs (%)	Water intake time (seconds)	Disintegration time (seconds)	Dissolution (%)
C1	97.66	12	25 to 45	92
C2	98.68	11	25 to 45	94
C3	97.45	9	20 to 45	95
C4	98.56	7	20 to 45	95
C5	99.45	6	15 to 35	98

5. Graphs of Result:

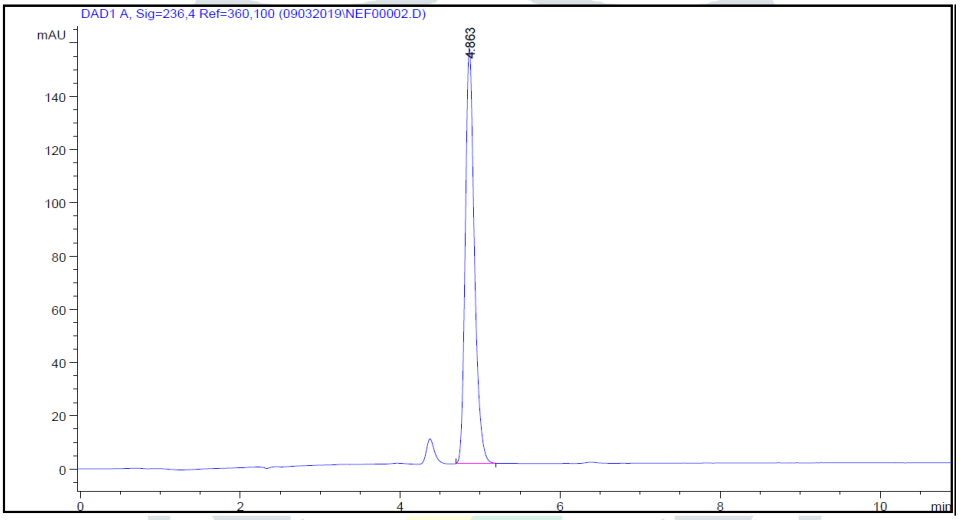
5.1. Nifedipine sample 30 mcg sample 01



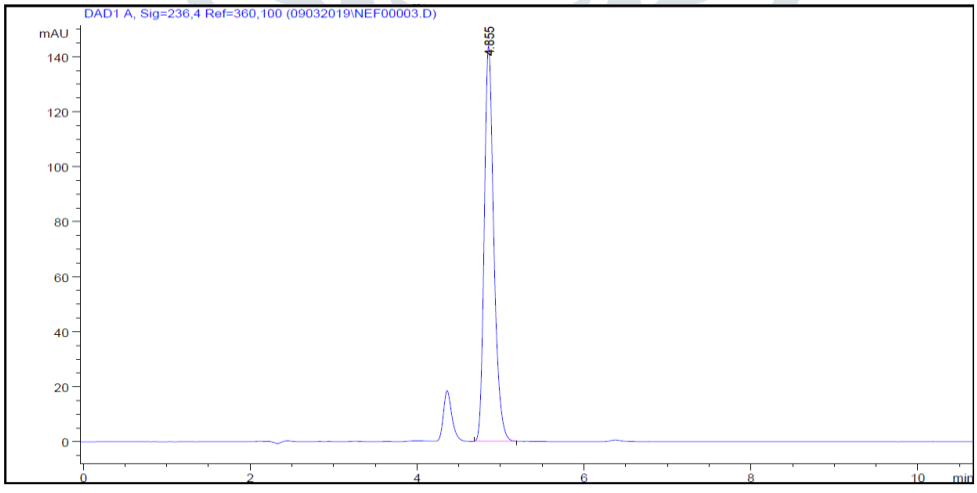
5.1.2 Nifedipine sample 30 mcg sample 02



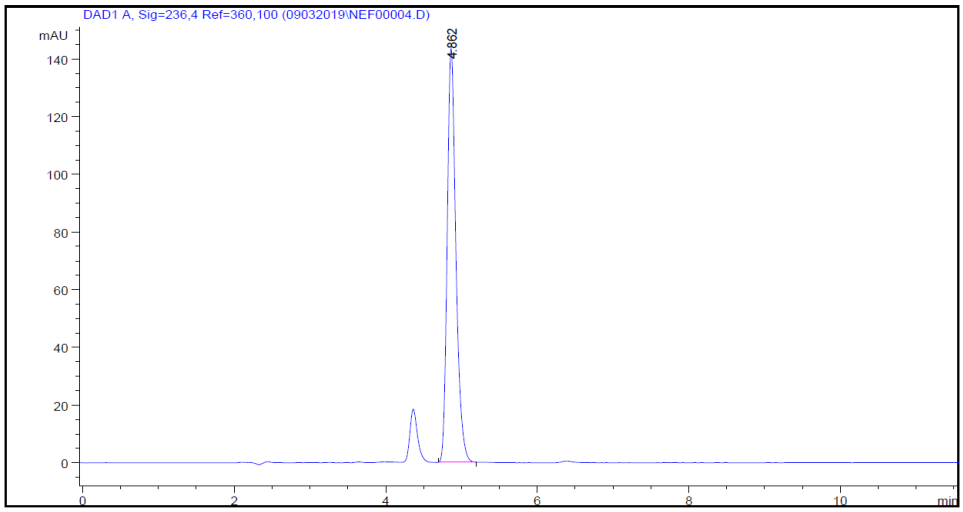
5.1.3 Nifedipine sample 30 mcg standard 01



5.1.4 Nifedipine sample 30 mcg standard 02



5.1.5 Nifedipine sample 30 mcg standard 03



6. Conclusion:

After the completion of this experiments the result obtained and we conclude that development of orodispersible Nifedipine formulation by using super disintegrants i.e. Cross carmillose sodium are given the result of dissolution more than mentioned in the Pharmacopeia. Some result are mentioned below:

1. Active drug Nifedipine with different excipient are stable viz Starch, Talcum, Mannitol, Lactose, Magnesium stearate, cross carmillose sodium and direct compressible starch.

2. Fast Disintegrating Nifedipine Tablets were successfully prepared by direct compression method.

3. The flow property of the granules and uniformity of the compressed tablet are better as compare the granules prepared by weight of dry granulation method or by slugging method.

4. The angle of repose of prepared granules are less than 30º which show the good quality of granules.

5. The hardness of compressed tablet by direct compression method are found in the rage of 3.5 to 4.5 kg/cm2.

6. The Thickness of the prepared tablets by all three methods was found between 3.5 mm. to 3.60 mm.

7. The Friability of the compressed tablet are within the range i.e. less than 1%. As the size of tablet are small.

8. The in vitro disintegration studies are found to be in 15 to 45 seconds. Formulation C5 showed in vitro disintegration time is 15 to 35 seconds.

9. On the basis of disintegration time formulation C5 which facilitate the faster disintegration in the mouth. The *in-vitro* percentage drug releases from fast dissolving tablets of Nifedipine prepared by direct compression method were found to be in the range of 99.45 %. Hence, finally it was concluded that the prepared oro dispersible tablets of Nifedipine 10 mg may prove to be potential candidate for effective fast disintegrating tablet dosage form.

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