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DEVELOPMENT AND EVALUATION OF SOLID DISPERSION MATRIX TABLET COMPRISING NIFEDIPINE WITH WATER SOLUBLE POLYMERS

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Abstract:

The basic aim of the present investigation is to formulate and evaluate solid dispersion matrix tablet dosage form which gives better utilisation of drug. In the present investigation, efforts were made to develop solid dispersion matrix tablets of Nifedipine, which will provide similar in-vitro release profiles to that of in-house specification drug release profiles which can be confirmedby calculating fl (difference/dissimilarity factor) and f2 (similarity factor). Nifedipine has a biological half life of 2-5 hours and it requires to be administered 2-3 times a day. In principle, drug candidate should have biological half life 2 to 8 hours to develop into sustained release dosage form. As Nifedipine is antihypertensive agent, a steady state concentration is necessary to maintain its optimal therapeutic activity. Thus, this soliddispersion matrix tablet maintaining steady state concentration for a prolonged period and will be a suitable candidate. The biopharmaceutical and physicochemical properties suggest that Nifedipine is suitable candidate to develop into solid dispersion matrix tablets.

Keywords: *Solid dispersion Matrix Tablet, Nifedipine, In-vitro release profiles, Biological half life.*

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1.INTRODUCTION[1-5]

A combination of solid dispersion and SR technique is one of the approach for supersaturation of drug can be applied by solid dispersion. The preparation of solid dispersions has become one of the most active areas of research in the pharmaceutical field with a view to improve the bioavailability of poorly soluble drugs. Sekiguchi and Obi (1961) developed a method to enhance the bioavailability of poorly water-soluble drugs, which was later termed solid dispersion. This method involved the formation of eutectic mixtures of drugs with water soluble carriers through the melting of their physical mixtures, which resulted in solubility enhancement and various methods are developed for solid dispersion like solvent evaporation, melting solvent and fusion method.

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be rate determining step for appearance of medicinal effect, therefore effortsto increase dissolution of drug with limited water solubility is often needed. Many methods are available to improve these characteristics, including salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of these methods, and involved a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method. Solid dispersion technique has been used for a wide variety of poorly aqueous soluble drugs such as nimesulide, ketoprofen, tenoxicam, Nifedipine, nimodipine using various hydrophilic carriers like polyethylene glycol, polyvinylpyrrolidone, hydroxypropyl methylcellulose, sugar, mannitol, urea etc.

In above combination of solid dispersion and SR technique, polymer as carriersystem can enhances the solubility of the poor water soluble drug and with use of polymer as matrix system can sustain the drug release.

The dissolution of solid dispersion tablets is rapid when the carrier is not dissolve very slow or very fast and when a drug is incorporated in the carrier at a relatively low drug load. Obviously, when the carrier dissolves slowly, the drug will also dissolve slowly. However, the slow dissolution rate of the drug when using fast dissolving carriers and/or formulations with high drug loads is considered less obvious.

In India, 2.3 million deaths were recorded caused by cardiovascular disease (CVD)in 1990, which may double by the year 2020. Thus, the management of CVD becomes very important to improve the health care system. Several drugs are being prescribed for the successful management of CVD, among the various drugs, Nifedipine a dihydropyridine derivative belongs to calcium channel blocker, is effectively being used drug in the management of various CVDs such as angina, mild to moderate hypertension, myocardial infarction, etc.

Nifedipine is chemically, dimethyl 2,6-dimethyl 1-4-(2-nitrophenyl)-1,4- dihydropyridine-3,5-dicarboxylate ($C_{17}H_{18}N_2O_6$).[18] The apparent half-life of Nifedipine is 2-4hours. Its dose is 5 to 20mg, 2-3 times in a day.[19] Calcium channel blocker Nifedipine, a antihypertensive drug is belong to class-II poorly water soluble drug, and its oral absorption is dissolution rate limited.

A numerous articles have been published on various aspects of solid dispersions, but despite promising early results on a laboratory scale, the commercial application of solid dispersion in dosage form design has been very limited and few products have been marketed.

The present study is aimed towards the formulation of a solid dispersion matrix tablet dosage form of Calcium channel blocker Nifedipine. As such sustained release productare needed for Nifedipine to prolong its duration of action and to improve patient compliance. SR products also avoid the vasodilator related adverse effects such as increase inheart rate, flushing and palpitations associated with conventional Nifedipine tablets. There are few reports on the formulation of sustained release products of Nifedipine employing coated granules, matrix tablets and microencapsulation.[20] so present study aimed towards the sustained release formulation of solid dispersion matrix tablets of Nifedipine.

In this study attempt is made to develop a potent therapeutic agent for cardiovascular disease, having half life 2-4 hrs, and which primarily reduce the occurrenceof steep rises in plasma concentration of drug, by using different polymers to achieve better bioavailability and also to reduce dosing frequency. The developed formulations are tested for *in vitro* drug release study and other parameters.
An overview on solid dispersion technology:

Poorly water-soluble drugs are increasingly becoming a problem in terms of obtaining the satisfactory dissolution within the gastrointestinal tract that is necessary for good bioavailability. It is not only

existing drugs that cause problems but it is the challenge of medicinal chemists to ensure that new drugs are not only active pharmacologically but have enough solubility to ensure fast dissolution at the site of administration, often gastrointestinal tract.

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilisation and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs.

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve improved solubility, increased dissolution rate, sustained release of drugs, altered solid state properties, and enhanced release of drugs from ointment, suppository bases. Solid dispersions are prepared by various methods like Fusion process, Solvent process, Fusion Solvent process and Supercritical fluid process.

Solid dispersion, the term refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly in amorphous particles (clusters) or in crystalline particles. The process of solubilisation involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction betweenthe solvent and the solute molecule or ion.

Types of solid dispersions[6-10]:

a) Simple eutectic mixture: A eutectic mixture of a sparingly water soluble drug and a highly water soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline component. The increase in surface area is mainly responsible for increased rate of dissolution. This led to a conclusion that the increase in dissolution was mainly due to decreased particle size.

b) Solid solutions: Solid solutions consist of a solid solute dissolved in a solid solvent. A mixed crystal is formed because the two components crystallize together in a homogenous one-phase system. Hence, this system would be expected to yield much higher rates ofdissolution than simple eutectic systems.

c) Glass solution of suspension: A glass solution is a homogenous system in which a glassy or a vitreous of the carrier solubilizer drug molecules in its matrix. PVP dissolved in organic solvents undergoes a transition to a glassy state upon evaporation of the solvent.

d) Compound or complex formation: This system is characterized by complexation of two components in a binary system during solid dispersion preparation. The availability of the drug from the complex is dependent on the solubility dissociation constant and the intrinsic absorption rate of the complex.

2.MATERIALS AND METHODS[10-15]:

2.1. MATERIALS USED

Nifedipine, HPMC K4M, HPC, Sodium alginate, PEG 4000, Avicel pH-105, Methanol, Talc.

2.2. METHODS USED

PREFORMULATION STUDIES

The following preformulation studies were performed for Nifedipine and polymers;

1. Determination of melting point of Nifedipine
2. Drug-excipient compatibility studies
   i. FT-IR Study
   ii. Differential Scanning Calorimetry (DSC) study
3. Saturation solubility of drug in phosphate buffer (pH 6.8) solution
4. Determination of Partition Coefficient
5. Determination of viscosity of polymers

1. Determination of melting point[16]:

Melting point was determined by taking small amount of Nifedipine in a capillary tube closed at one end. The capillary tube was placed in an electrically operated melting point apparatus and the temperature at which the drug melts was recorded. This was performed thrice and average value was noted.

2. Drug-excipient compatibility study[17]:

FT-IR Study: In the preparation of tablets formulation, drug and polymer may interact as they are in close contact with each other, which could lead to the instability of drug. Preformulation studies regarding the drug-polymer interaction are therefore very critical in selecting appropriate polymers. FT-IR (8700) spectroscopy was employed to ascertain the compatibility between Nifedipine and selected polymers. The pure drug and drug with excipient were scanned separately. Potassium bromide was mixed with drug and/or polymerin 9:1 ratio and the spectra were taken. FT-IR spectrum of Nifedipine was compared with FTIR spectra of Nifedipine with polymer. Disappearance of Nifedipine peaks or

shifting of peak in any of the spectra was studied.

Differential Scanning Calorimetry (DSC) Study: DSC analysis of pure drug, and optimized formulation was performed with Shimadzu DSC TA60 thermal analyser at the heating flow rates of 5 °C per min between 50 and 300 °C under static air using aluminium pans.

PHYSICAL PROPERTIES[15-18]

1. Angle of Repose: The angle of repose values of Nifedipine and the granules were determined by the funnel method (Reposogram). The accurately weighed drug or granules was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the granules cone was measured and angle of repose was calculated using the following equation;

$$0 = \tan^{-1} (h/r)$$

EVALUATION OF NIFEDIPINE TABLETS[18-20]

The tablets after punching of every batch were evaluated for in process and finished product quality control tests i.e. appearance, dimensions (diameter and thickness), weight variation, hardness, friability, drug content, and *in vitro* drug release.

Appearance:

The tablets were checked for presence of cracks, depressions, pinholes etc if any, uniformity of the color, and the polish of the tablet.

Dimensions:

Thickness and diameter of a tablet were measured using digital vernier callipers. These values were checked and used to adjust the initial stages of compression.

Weight Uniformity Test:

Twenty tablets were weighed individually and all together. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (± 10%).

Hardness Test:

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufactures and with the different types of tablets. The hardness was tested using Monsanto tester. "Hardness factor", the average of the six determinations, was determined and reported. The force was measured in kilograms per centimeter square.

3.RESULTS AND DISCUSSION:

Table-1- Formulations of Nifedipine solid dispersion matrix tablets

Ingredients / Formulation'	Nifedipine : PEG4000 (1:1) (mg)	HPMC K4M (mg)	HPC (mg)	Sodium alginate (mg)	Avicel (mg)	Mg. stearate (mg)	Talc (mg)
F-I	40	20	10	3	42	2.5	2.5
F-II	40	40	10	3	22	2.5	2.5
F-III	40	20	30	3	22	2.5	2.5
F-IV	40	40	30	3	02	2.5	2.5
F-V	40	20	20	1	34	2.5	2.5
F-VI	40	40	20	1	14	2.5	2.5
F-VII	40	20	20	5	30	2.5	2.5
F-VIII	40	40	20	5	10	2.5	2.5
F-IX	40	30	10	1	34	2.5	2.5
F-X	40	30	30	1	14	2.5	2.5
F-XI	40	30	10	5	30	2.5	2.5
F-XII	40	30	30	5	10	2.5	2.5
F-XIII	40	30	20	3	22	2.5	2.5
F-XIV	40	30	20	3	22	2.5	2.5
F-XV	40	30	20	3	22	2.5	2.5

Table-2-Physical properties of formulation blend

Parameter / Formulation	Bulk density (gm/cc)	Tapped density (gm/cc)	Angle of repose 0 (^{0})	Compressibility index (%)	Hausner's ratio
F-I	0.336	0.492	29.51	31.70	1.46
F-II	0.344	0.516	31.32	33.33	1.50
F-III	0.348	0.516	33.61	32.55	1.48
F-IV	0.369	0.569	34.28	34.45	1.52
F-V	0.340	0.500	29.47	32.00	1.47
F-VI	0.360	0.534	33.11	32.58	1.48
F-VII	0.344	0.508	29.47	32.28	1.47
F-VIII	0.356	0.543	32.00	34.43	1.52
F-IX	0.340	0.484	27.47	29.75	1.43
F-X	0.356	0.534	31.32	33.33	1.50
F-XI	0.340	0.492	30.25	30.89	1.44
F-XII	0.360	0.543	31.22	33.70	1.50
F-XIII	0.344	0.508	31.32	32.28	1.47
F-XIV	0.344	0.516	31.32	33.33	1.50
F-XV	0.348	0.508	31.32	31.49	1.45

Table-3-Post Compressional Parameters of Prepared tablets

Parameter / Formulation	Uniformity of weight (% deviation)#	Hardness (Kg/cm^2)*	Friability (%)#	Drug content (%)*	Thickness (mm)*	Diameter (mm)*
F-I	1.21 ± 0.84%	3.5 ± 0.05	0.77 ± 0.01	96.60 ± 0.17	2.97 ± 0.05	6.03 ± 0.05
F-II	1.52 ± 0.93%	4.5 ± 0.00	0.67 ± 0.02	97.11 ± 0.13	3.00 ± 0.00	6.10 ± 0.10
F-III	1.28 ± 0.52%	5.1 ± 0.10	0.62 ± 0.00	95.55 ± 0.24	3.00 ± 0.00	6.13 ± 0.05
F-IV	1.38 ± 0.96%	5.4 ± 0.05	0.65 ± 0.02	95.50 ± 0.09	3.00 ± 0.00	6.00 ± 0.00
F-V	1.33 ± 1.06%	4.0 ± 0.00	0.76 ± 0.09	92.55 ± 0.24	3.03 ± 0.05	6.00 ± 0.00
F-VI	2.24 ± 1.46%	4.6 ± 0.10	0.74 ± 0.06	99.40 ± 0.13	3.00 ± 0.00	6.10 ± 0.10
F-VII	2.30 ± 1.79%	4.1 ± 0.10	0.77 ± 0.01	95.70 ± 0.39	3.10 ± 0.05	6.00 ± 0.00
F-VIII	1.58 ± 1.58%	4.2 ± 0.20	0.63 ± 0.07	92.65 ± 0.12	3.00 ± 0.00	6.00 ± 0.00
F-IX	0.55 ± 0.37%	3.5 ± 0.05	0.78 ± 0.01	92.80 ± 0.17	2.90 ± 0.10	6.10 ± 0.10
F-X	0.98 ± 0.82%	4.5 ± 0.00	0.66 ± 0.01	93.20 ± 0.28	3.00 ± 0.00	6.00 ± 0.00
F-XI	1.24 ± 0.84%	4.0 ± 0.00	0.78 ± 0.01	94.75 ± 0.17	3.00 ± 0.00	6.00 ± 0.00
F-XII	0.95 ± 1.12%	4.5 ± 0.00	0.64 ± 0.02	92.55 ± 0.24	2.96 ± 0.04	6.03 ± 0.05
F-XIII	1.54 ± 0.96%	4.3 ± 0.05	0.75 ± 0.06	98.60 ± 0.57	3.00 ± 0.00	6.00 ± 0.00
F-XIV	1.54 ± 0.96%	4.3 ± 0.00	0.75 ± 0.06	97.10 ± 0.02	3.10 ± 0.05	6.00 ± 0.00
F-XV	1.52 ± 0.93%	4.3 ± 0.00	0.74 ± 0.06	97.70 ± 0.27	3.00 ± 0.00	6.03 ± 0.05

Table-4- Dissolution profile for the batches F-I to F-XV

Time (hrs.)	Percentage drug release (%)														
	F-I	F-II	F-III	F-IV	F-V	F-VI	F-VII	F-VIII	F-IX	F-X	F-XI	F-XII	F-XIII	F-XIV	F-XV
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	12.63	17.46	12.92	20.24	14.68	23.02	18.48	12.34	17.61	15.56	16.29	18.63	13.21	13.21	13.21
2	23.61	46.00	27.85	35.17	31.21	45.85	36.63	22.14	35.02	31.21	33.41	26.09	24.09	24.19	24.09
3	39.26	62.09	43.51	48.04	44.82	64.29	58.14	35.02	46.00	41.31	44.82	40.14	39.41	39.41	39.26
4	56.39	75.98	64.73	66.92	64.43	87.56	73.95	53.31	69.70	50.97	63.41	59.90	48.92	49.65	48.63
6	77.46	81.56	80.09	73.95	84.63	92.68	85.59	73.21	86.60	64.58	77.17	72.78	63.85	63.56	63.41
8	86.09	91.36	87.80	90.34	87.41	98.39	88.29	86.24	92.39	74.53	86.09	77.75	73.65	74.09	73.21
10	91.51	95.02	91.36	93.26	90.92	-	94.29	91.21	-	86.82	93.41	86.09	84.78	85.07	84.63
12	94.58	-	94.73	-	94.00	-	-	-	-	92.82	-	-	97.21	96.48	96.19

Table-5-*In vitro* release of Nifedipine tablets from F-XIII

Time (h)	Absorbance AM ± SD	Concentration (Pg/ml)	Dilution factor	Amount in 900 ml (mg)	Cumulative amount of drug released (mg)	Cumulative amount of drug unreleased (mg)	% cumulative drug released	log % cumulative drug released	% cumulative drug remain unreleased	log % cumulative drug remain unreleased
0	0.000 ± 0.000	0	0	0	0	0	0	0	100	2
1	0.091 ± 0.001	1.468	2	2.643	2.643	17.357	13.21	1.121	86.79	1.938
2	0.165 ± 0.002	2.672	2	4.809	4.838	15.162	24.19	1.3836	75.81	1.880
3	0.270 ± 0.005	4.379	2	7.882	7.935	12.065	39.67	1.5985	60.33	1.781
4	0.335 ± 0.006	5.936	2	9.785	9.873	10.127	49.36	1.6934	50.64	1.704
6	0.437 ± 0.003	7.094	2	12.770	12.879	7.121	64.39	1.8088	35.61	1.552
8	0.504 ± 0.003	8.184	2	14.731	14.874	5.126	74.37	1.8714	25.63	1.409
10	0.580 ± 0.006	9.420	2	16.956	17.121	2.879	85.6	1.9325	14.4	1.158
12	0.665 ± 0.001	10.802	2	19.443	19.633	0.367	98.16	1.9919	1.84	0.265

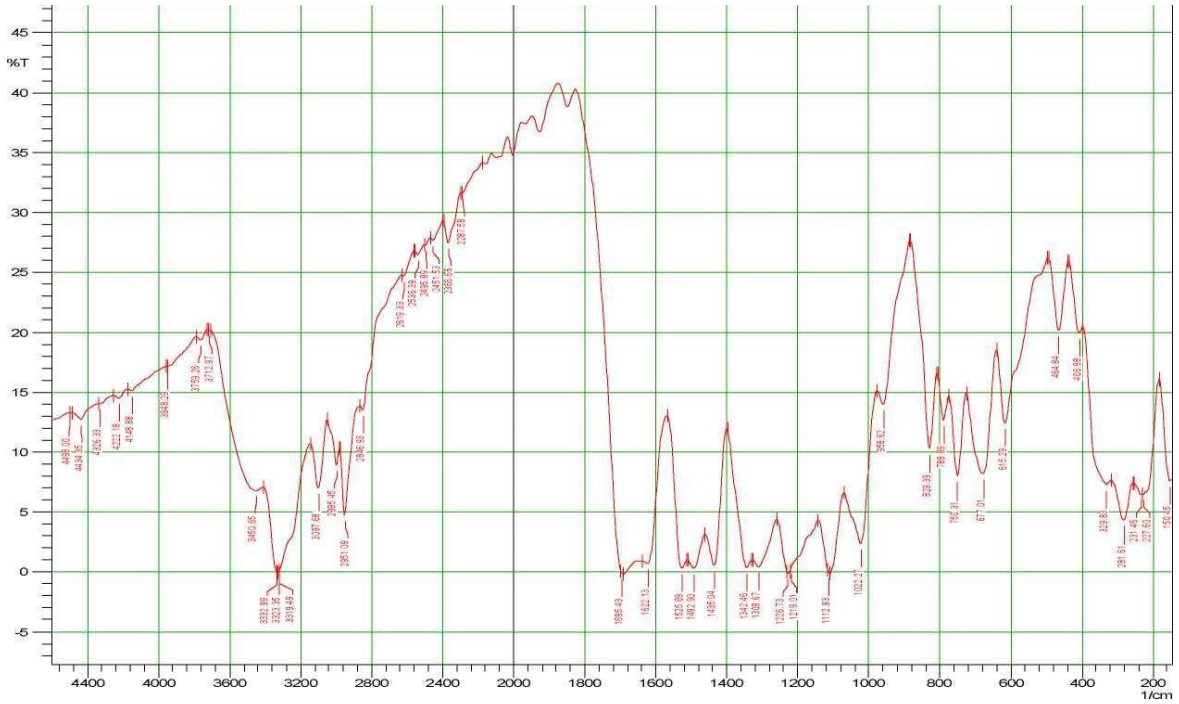

Figure 1: FT-IR spectrum of Nifedipine

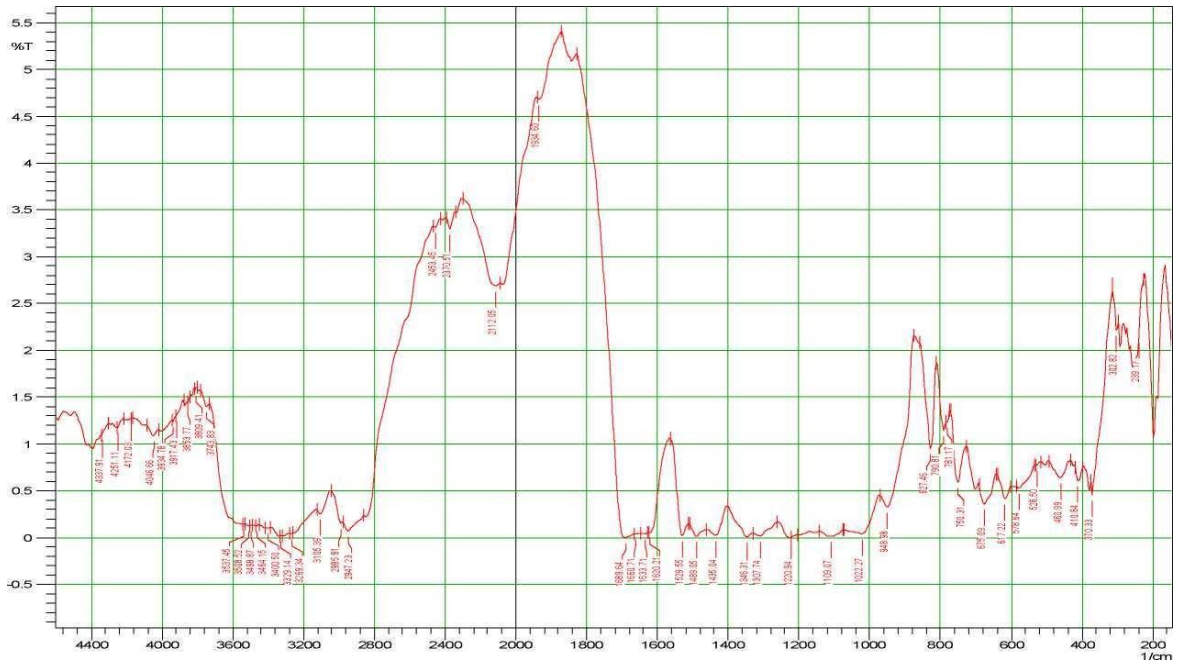

Figure 2: FT-IR spectrum of Nifedipine with HPMC

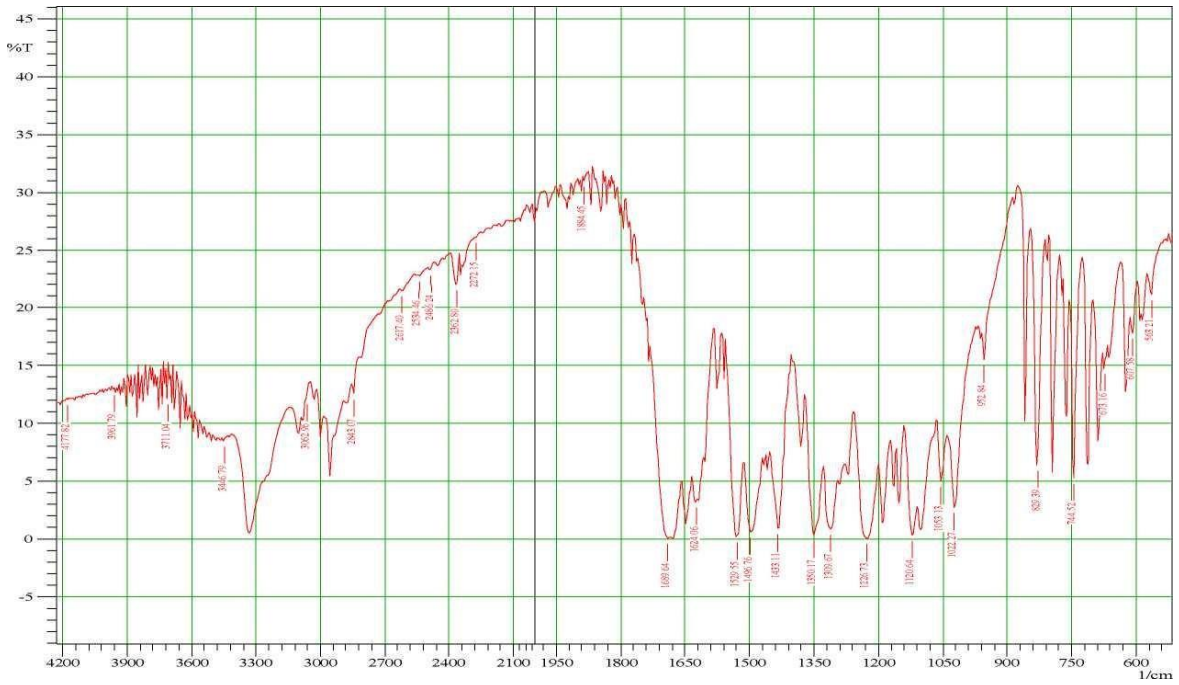

Figure 3: FT-IR spectrum of Nifedipine with HPC

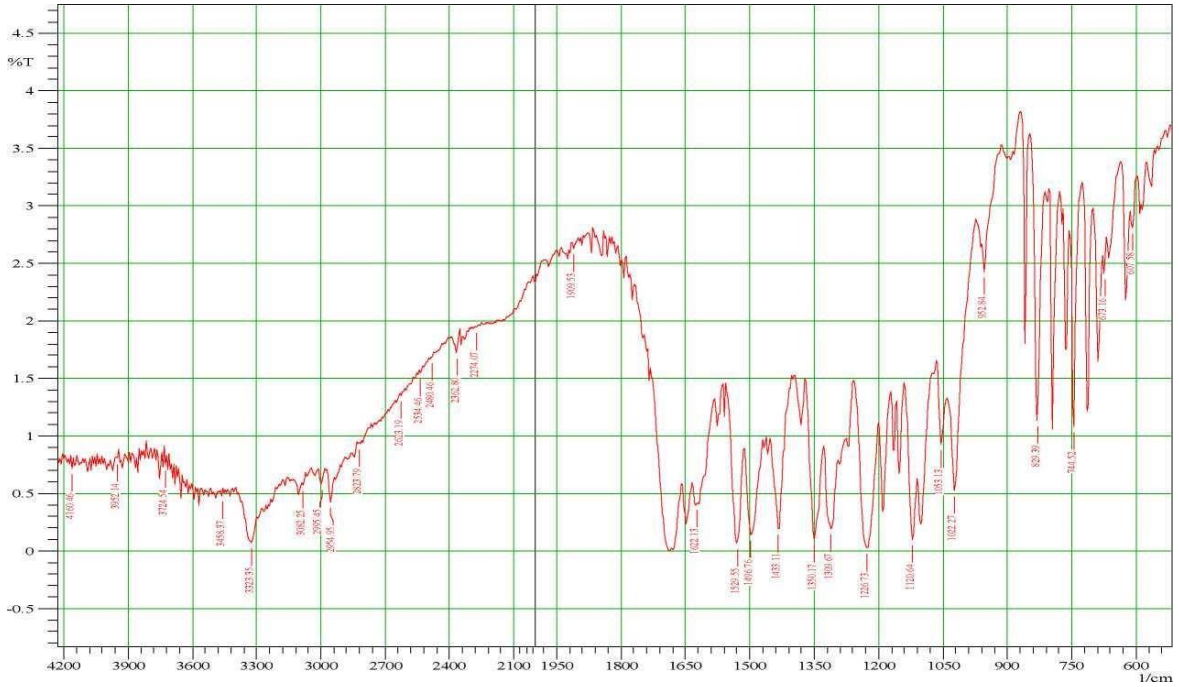

Figure 4: FT-IR spectrum of Nifedipine with Sodium Alginate

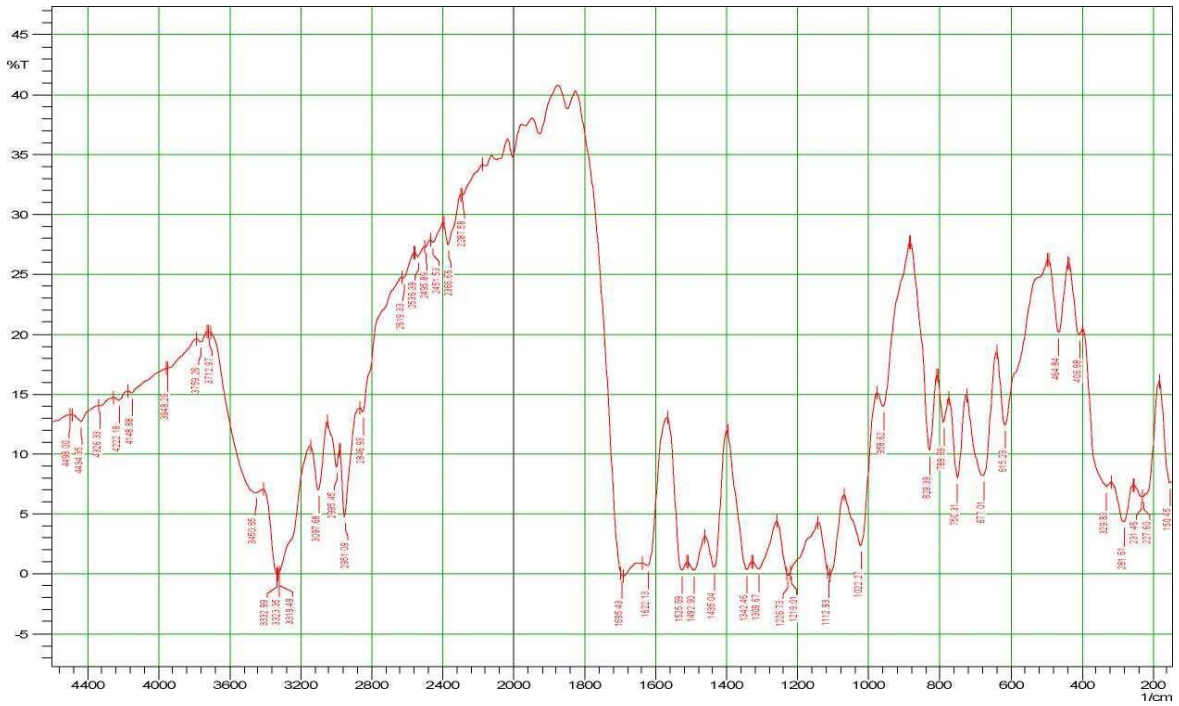

Figure 5: FT-IR spectrum of Nifedipine with all Excipients

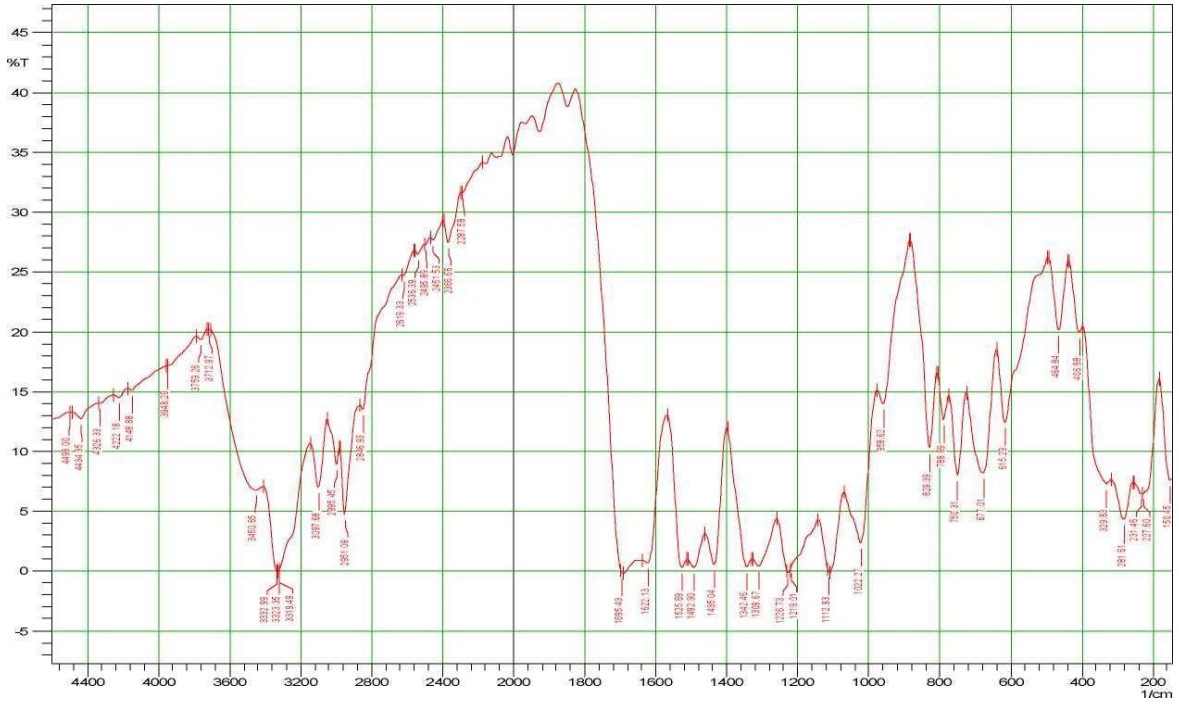

Figure 6: FT-IR spectrum of Final Formulation

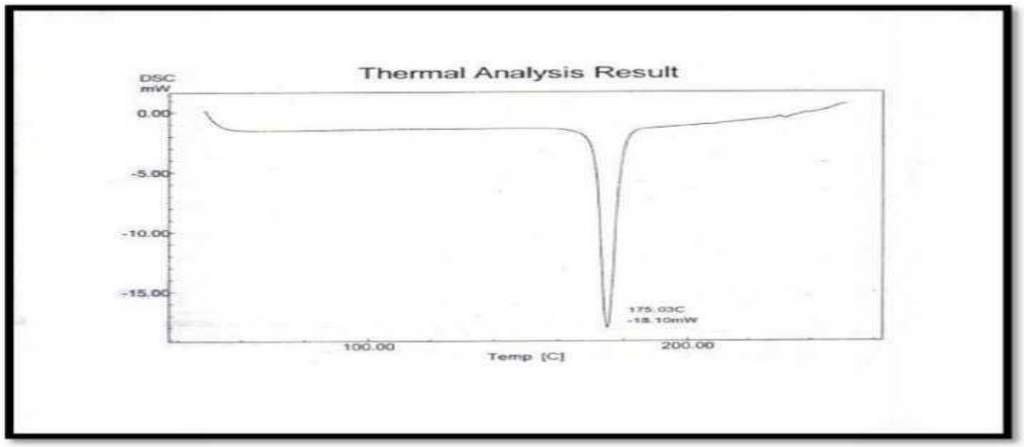

Figure 7: DSC of Nifedipine

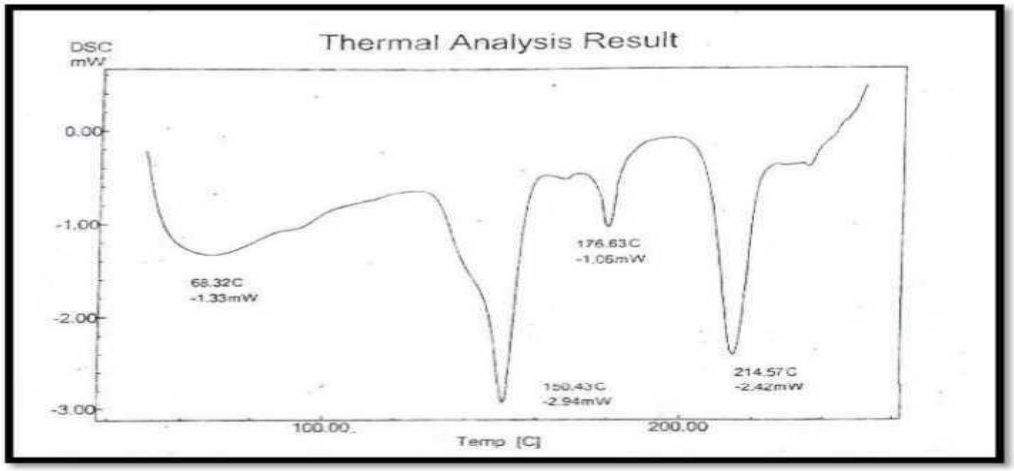

Figure 8: DSC of Final Formulation

4.CONCLUSION:

Suitable analytical method based on UV-Visible spectrophotometer was developed for Nifedipine. Lamada max of 238 nm was identified in 0.1N HCl solution and phosphate buffer solution, pH 6.8.From the FT-IR spectra and thermal analysis (DSC), the interference was verified and found that Nifedipine did not interfere with the excipients used. Procedure to manufacture solid dispersion matrix tablets by direct compression was established and Matrix tablets of Nifedipine (F-I to F-XV) were successfully prepared by direct compression method. The tablets were evaluated for pharmacopoeial and non-pharmacopoeial tests. Based on the results the formulations F-XIII, F-XIV, and F-XV were identified as better formulations amongst all formulations developed. *In vitro* release profiles of optimized formulations of Nifedipine matrix tablets (F- XIII, F-XIV, and F-XV) were found to be similar to that of in house specification drug release profile. The f1 and f2 values for the comparison of release of drugs fromthe formulations F-XIII, F-XIV, and F-XV with the theoretical drug release profile were found to be for F-XIII 5.06 and 82.09 respectively, for F-XIV 5.62 and 81.31 respectively, and for F-XV 4.74 and 82.83 respectively. The earlier three batches contain same concentration of polymers and other excipients such as 30mg HPMC, 20mg HPC, and 3mg sodium alginate. Their release profiles were found to be nearly same at every hour so further studies was done on one of the batch out of three (F- XIII).

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