World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Published by Atom and Cell Publishers
Available online at: http://www.wjpsonline.com/
Research Article

Formulation and Evaluation of Solid dispersion for Dissolution Enhancement of Nifedipine

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Received: 29-01-2014 / Revised: 08-02-2014 / Accepted: 15-02-2014

ABSTRACT

Nifedipine, a calcium channel blocker antihypertensive drug, is a poorly water soluble drug and belongs to BCS class II. The objective of the research work was to formulate and optimize solid dispersions (SDs) of a poorly water soluble drug, nifedipine, with sodium starch glycollate, croscarmellose sodium, eudragit E-100. Solid dispersions were prepared by solvent evaporation techniques in different weight ratios of polymers. The results indicated that homogeneous or heterogeneous conditions during the preparation methods employed governed the internal structures of the polymer matrices while retaining the drug in an amorphous form. The physical mixtures and solid dispersions were subjected to drug content and dissolution test. The best formulation, nifedipine with croscarmellose sodium in 1:7 ratio, among all was further adsorbed on neusilin US2 to form ternary mixture. The increased dissolution was achieved by more than 70percent and 30percent comparatively to the nifedipine API and marketed product respectively. The tablet dosage form prepared from ternary mixture was stable at stressed conditions 40±2°C and 75±5% RH. The release kinetics of drug from formulation and marketed product follows peppas model. The similar factor f2 was within limit for the product at stressed conditions with the product at room temperature at the same time.

Keywords*:* Croscarmellose sodium, Dissolution enhancement, Eudragit E-100, Neusilin US2, Nifedipine, Sodium starch glycollate, Solid dispersion, Ternary mixture, Stability study, Similarity factor

INTRODUCTION

The Biopharmaceutics Classification System (BCS) is the scientific framework classifies drug substances based on their aqueous solubility and intestinal permeability. Dissolution and gastrointestinal permeability are the fundamental parameters controlling rate and extension of drug absorption[1][2][3][4][5]. The molecules with 10mg/ml or lesser solubility in water over the pH 1 to pH 7 at 37ºC exhibit the maximum bioavailability problems. Biopharmaceutical Classification System (BCS) Class II drugs (e.g. glipizide, nifedipine, itraconazole, aceclofenac etc.) are those with solubilities and dissolution rate too low to be consistent with complete absorption, even though they are highly membrane permeable. Maximum molecules developed today are with lesser aqueous solubility and required to improve the solubility and dissolution to get absorb. Various methods e.g., micronization, stabilization of high energy states, inclusion of surfactants, formulation as emulsion or microemulsion systems, salt formation, solvent deposition, ordered mixing, cyclodextrin complexation, solid dispersions etc. are available to increase the solubility and dissolution rate of the Class II drugs so that absorption and thus bioavailability of the formulation can be improved[6]. The solid dispersion (SD) approach, to reduce particle size and therefore increase the dissolution rate and absorption of drugs, was first recognized in 1961.The term SD refers to the dispersion of one or more active ingredients in an inert carrier in a solid state[7].

Nifedipine (dimethyl 1, 4-dihydro-2, 6-dimethyl-4-(2-nitrophenyl) pyridine-3, 5-dicarboxylate or 1-Dihydro-2, 6-dimethyl-4-(2-nitrophenyl)-pyridin-3, 5-dicarboxylic acid-dimethyl ester), represented in figure 1, is a calcium channel blocker antihypertensive drug. Nifedipine is freely soluble at 20°C in acetone (250g/l), in methylene chloride

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(160g/l), in chloroform (140g/l), soluble in ethyl acetate (50g/l), slightly soluble in methanol (26g/l) and ethanol (17g/l) and practically insoluble in water[8][9][10]. Several approaches has been use to enhance the dissolution of nifedipine. The solid dispersion with poloxomer 407 [11], polyethylene glycol 400[12], PEG 1500, polyvinylpyrrolidone (PVP 30, PVP 12), polyvinylpyrrolidone-co-vinylacetate (PVPVA), Eudragit EPO[13], mannitol[14], Hydroxypropylmethylcellulose HPMC[15], PVP and PEG, inclusion complex with beta cyclodextrin (Bcyd)[16] co-grinding by a roll mill and high-pressure homogenization without any organic solvent using lipid (Hydrogenated soybean phosphatidyl-choline (HSPC):dipalmitoyl phosphatidyl-glycerol (DPPG)= 5:1 molar ratio)[17], co-grinding with PEG 6000and HPMA[18], microparticles containing nifedipine (NIF) in the range of 25–75% w/w using poly (sodium methacrylate, methyl methacrylate) (Na PMM)[19], nanosuspension[20], micronization[21] were prepared for dissolution enhancement of nifedipine.

Neusilin is a fine white powder or granule of magnesium aluminometasilicate manufactured by Fuji Chemical Industry. Compared to other common excipients in the silicate family, Neusilin's superior physico-chemical properties can resolve formulation problems encountered with oily actives, improve the quality of tablets, powder flow, capsules and many more[22]. The surface adsorption phenomenon of the neusilin to the solid dispersion has been proved[23][24][25][26].

The solid dispersion thus formed further used for formation of ternary mixture with neusilin US2, as has been utilized for study of some another drug(s). This approach may be useful for this model drugs for enhancement of the solubility and dissolution rate.

MATERIALS AND METHODS

Materials: Nifedipine I.P. was obtained ex-gratis from Vijay Perfumes Pvt Ltd., Vasai (W), India. Sodium starch glycollate (SSG) and croscarmellose sodium (CCM) was obtained ex-gratis from Maple Biotech Pvt Ltd., Pune,. Eudragit E-100, Neusiline US2 were obtained ex gratis from Evonik Degussa India Pvt. Ltd. Mumbai and Gangwal Chemicals Pvt. Ltd. Mumbai India respectively. All other chemical and reagents were of analytical grade.

Drug Excipient Compatibility Studies: Nifedipine and excipients (Sodium starch glycollate, Croscarmellose sodium, Eudragit E 100 and Neusiline US2), previously passed through sieve number 60, were taken in 1:1 ratio. Sealed capillary tube was used to mix the components in a glass vial (5 ml). The glass vials were protected from light by covering with aluminum foil. The samples were kept at 50°C for one month. FTIR spectra were taken for entire samples immediately after mixing and after one month storage at 50°C.

Standard Calibration Curve: Accurately weighed (2.5mg) nifedipine was dissolved in approximately 5 ml of Hydrochloric Acid Buffer pH 1.2. The volume was then made upto the mark in 100 ml volumetric flask with hydrochloric acid buffer pH 1.2. This stock solution (25µg/ml) was diluted with hydrochloric acid buffer pH 1.2 to prepare solutions of known concentrations, in duplicates, in the range of 5–25µg/ml. One of the prepared solutions was analyzed for maximum (λmax) absorbance in UV spectrophotometer. All the prepared solutions of known concentrations were analyzed for absorbance at 236 nm λmax[27][28].

Preparation of Formulations

Physical mixtures: Physical mixtures were prepared by blending in a glass mortar of accurately weighed quantities of nifedipine and carrier(s) for about 10 min in different ratio, mentioned in table 1, and stored in desiccators over fused calcium chloride after passing through sieve no.44. **Solid dispersion**: The required amount of drug and the carriers, as shown in table 1, were dissolved in sufficient volume of acetone with continuous stirring. The solvent was then completely evaporated with vacuum oven at 40°C to obtain dry mass. The dried mass was pulverized passed through 44 mesh sieve and stored in desiccators until used for further studies[29][30][31][32].

Drug content studies: The drug content was calculated by dissolving nifedipine API, physical mixtures and solid dispersion of nifedipine equivalent to 5mg in a 100ml of methanol. The solution was filtered through 0.45µ filter membrane and assayed further by using UV double beam spectrophotometer at 236nm. Three replicates were prepared, and the average drug contents were estimated[33].

Determination of *in vitro* drug release: The nifedipine API, marketed preparation, physical mixture and solid dispersion equivalent to 5mg of drug added in dissolution media. The dissolution study was carried out using USP apparatus type-II. The dissolution medium was 500 ml hydrochloric acid buffer pH 1.2 kept at 37±0.5ºC. The paddle was rotated at 100 rpm. Samples of 5 ml were withdrawn at specified time intervals and analyzed by UV Visible spectrophotometer Shimadzu-1700 at 236nm. The samples withdrawn were replaced by fresh buffer solutions to maintain sink condition. Each preparation was tested in triplicate

and then means values were calculated. The dissolution study was continued for 60min[12][34][35][32].

Formation of Ternary Mixture

The best preparation among the twenty four formulations was selected and further absorbed on Neusiline US2 in 1:1 ratio by milling for 10min in mortar pestle to prepare ternary mixture. The dried mass was passed through 44 mesh sieve and stored in desiccators until used for further studies[23][36][25][26][37][38].

Evaluation of Ternary Mixture

Percentage practical yield, drug content and *in vitro* drug release was determination.

Formation and Evaluation of Powder Blend for Tabletting of Ternary Mixture

Formation of powder blend

The accurately weighed quantities of the ingredients, passed through 44 mesh sieve, mentioned below in table 2, were taken. All the ingredients were properly mixed. Finally talc and magnesium stearate were then added and again mixed for 5 minutes so that particle surface was coated by lubricant evenly. The precaution was taken for the light sensitive drug during experimentation[32][39][40].

Evaluation of powder blend

The prepared powder blend was evaluated for micromeritic characterizations.

Angle of repose: Angle of repose determined by following equation: $\theta = \tan^{-1}(h/r)$

Where, h = height of pile, r = radius of the pile base

Approximately 5 gm. of powder blend prepared for tablet is transferred into the funnel and powder emptied from the funnel making a pile whose radius and height is measured using a scale[33][40][41].

Bulk density: The bulk density was calculated using equation: $\rho b = M/V$

Where, ρb = Bulk density, M = Mass of the powder blend in grams

V = Final untapped volume of powder blend in ml.

Tapped density: The tapped density was calculated using equation: $\rho t = M/Vp$

Where, ρt = tapped density, M= Mass of powder blend in grams, Vp= Final tapped volume of powder blend in ml or cm^3.

Weighed amount is introduced into the USP bulk density apparatus type-1 and the volume of powder blend noted. Switch on the apparatus, note the volume of powder blend after 500, 750 and 1250 taps and calculate the tapped density using above formula[33][40][41].

Hausner Ratio: It is an indirect index of ease of powder flow. It is calculated from tapped and bulk density by using following formula[40]

Hausner Ratio (HR) = Tapped density/Bulk density

Compressibility index: The simplest way for measurement of flow of the powder is its compressibility, an indication of the ease with which a material can be induced to flow. It is expressed as compressibility index (CI). It is calculated from tapped and bulk density by using following formula. It is also known as carr's compressibility index or carr's index[33][40][41].

Carr's index (%) = (Tapped density – Bulk density) ×100/Tapped density

Tablet Formulation and Evaluation

Tablet Formulation

The accurately weighed quantity of the ingredients, passed through 44 mesh sieve, mentioned above in table 2 was taken. The ternary mixture for nifedipine was weighed for equivalent quantity of nifedipine to 5mg. All the ingredients were properly mixed. Finally talc and magnesium stearate were then added and again mixed for 5 minutes so that particle surface was coated by lubricant evenly. The resulting blend was compressed to form 250mg tablet by punches using 8mm round shaped dies to form round flat faced tablets[42][32][43][39].

Tablet Evaluation: The prepared tablets were evaluated for different pharmacopoeial and non pharmacopoeial test.

Evaluation of Release Kinetics of Tablet

Model independent and model dependent parameters are calculated.

Model Independent Parameters: The dissolution efficiency and mean dissolution time is calculated

Dissolution Efficiency (DE)

Dissolution efficiency (*DE*) represents the area under the dissolution curve at time *t* (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100 % dissolution in the same time. Dissolution efficiency was calculated at 60 minutes using the following formula.

$$D.E._{60} = \frac{0.5 \times \%\ drug\ release\ at\ 60\ min}{Total\ \%\ drug\ release} \times 100$$

Model Dependent Parameters

Data obtained from *in vitro* release studies was fitted to various kinetics equations to find out the mechanism of release of drug from the formulation compared to the marketed preparation. The kinetics models used were Zero order, First order, Hixon croswell model, Higuchi and Peppas model.

Stability Testing

The stability testing is performed to confirm that whether the drug content or drug product varies with time under the effect of environmental factor such as temperature, humidity and light, and to establish a retest period for the drug substance or a self life for the drug product and recommended storage conditions. Twenty tablets of nifedipine were wrapped individually in aluminum foil and kept in the equipment for three months at 40±2°C and 75±5% Relative Humidity (RH). One set of tablet was kept at room temperature (RT) at the same time. The desired temperature and humidity was set. These tablets were examined for physical appearance and cumulative percent release[39][44][45][46].

Evaluation after stability study

The product was evaluated after keeping the product at specified temperature and relative humidity. The product kept at accelerated temperature and humidity was compared with the product kept at the room temperature.

Physical Appearance: The both the tablet products kept at different conditions were observed for the physical appearance.

Dissolution Test: Three tablets were taken from the humidity cum stability chamber after three months and evaluated in vitro for release profile.

Dissolution profile comparison by determination of similarity factor f2 for product kept at stress condition and normal conditions: Among several methods investigated for dissolution profile comparison, f2 is the simplest.

$$f_2 = 50 \cdot \log\{[1+(1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \cdot 100\}$$

where Rt and Tt are the cumulative percentage dissolved at each of the selected n time points of the reference and test product respectively. The factor f2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time-points. The factor f2 measures the closeness between the two profiles. Because of the nature of measurement, f2 was described as similarity factor. In dissolution profile comparisons, especially to assure similarity in product performance, regulatory interest is in knowing how similar the two curves are, and to have a measure which is more sensitive to large differences at any particular time point. For this reason, the f2 comparison has been the focus in FDA guidance document. When the two profiles are identical, f2=100. An average difference of 10% at all measured time points results in a f2 value of 50. FDA has set a public standard of f2 value between 50-100 to indicate similarity between two dissolution profiles[47][48][49][50][51].

RESULTS AND DISCUSSION

Nifedipine Preformulation Studies

Drug-Excipient Compatibility Studies: The FTIR spectra of nifedipine and excipients (Sodium starch glycollate, Croscarmellose, Eudragit E 100 and Neusilin US2) mixture at immediate and stress conditions show that there is stability and identity to the reference spectra. Characteristic peaks of nifedipine were not affected and prominently observed in FTIR spectra of nifedipine along with polymers. There was no physical change in drug and mixtures even after 30days, which indicates the absence of physical incompatibility as reported in figure 2 to figure 6.

Standard Calibration Curve: The standard calibration curve were prepared and represented in figure 7 and figure 8.

Preparation and Evaluation of Formulations

Preparation of formulations

Physical Mixtures: Physical mixtures prepared were slight yellowish in colour. The formulation were prepared and stored in glass vials surrounded by aluminum foil in desiccator.

Solid Dispersion: Solid dispersions prepared by solvent evaporation method were slight yellowish and odourless. The formulations were stored in glass vials surrounded by aluminum foil in desiccators.

Evaluation of formulations

Drug Content: The drug content calculated for all the formulated physical mixtures, solid dispersions including nifedipine active pharmaceutical ingredient (API) and marketed preparation was between 96.55±0.004 to 100.41±0.009 which is within acceptable limit.

Dissolution study of nifedipine API, marketed product, physical mixtures and solid dispersions of nifedipine: The comparative cumulative percentage release of pure nifedipine API, marketed product (MP), physical mixtures and

solid dispersions is mentioned in table 3. The overall observations from the release data reveals that the croscarmellose sodium in ratio of seven times to the drug improves the release of the drug form the formulation comparatively greater than sodium starch glycollate and Eudragit E100. The high swelling efficiency improves the release of the nifedipine from the formulation. Thus it was concluded that the SD8 formulation having nifedipine and croscarmellose sodium in 1:7 ratio, have greater percentage practical yield in solid dispersion and highest percentage release of the drug among all the formulations. The SD8 formulation was selected on these bases for further formation of the ternary mixture with neusilin US2.

Formation of ternary mixture

The best preparation among the twenty four formulations i.e. SD8 was absorbed on Neusiline US2 in 1:1 ratio by milling for 10min in mortar pestle to prepare ternary mixture.

Evaluation of ternary mixture

Physical Appearance: The appearance of the ternary mixture was slightly yellowish.

In vitro drug release from the ternary mixture:

In vitro drug release from ternary mixture was further increased from the SD8 formulation as shown in table 4 and figure 9. The increase in the drug release may be attributed to the characteristics of Neusiline. Neusilin US2 is amorphous, possesses very large specific surface area. This character emphasizes that the solid dispersion may adsorb on the surface of the neusilin US2 and dissolve rapidly. The presence of silanols on its surface makes it a potential proton donor as well as a proton acceptor.

The formation of hydrogen bond was previously reported by Gupta et al. on co-grinding carboxylic acid containing drugs such as indomethacin, ketoprofen, naproxen, and progesterone with Neusilin US2. The nifedipine has limited proton acceptor property with its ester group, that also make a possibility of formation of H-bonds between neusiline and solid dispersion of nifedipine formulated with crosscarmellose. The physical and chemical stability of the amorphous state of drug-neusilin US2 complexes is well documented. Neusilin US2 remains flowable even after absorbing moisture up to 250% of its weight[24][26].

DSC thermograph of Nifedipine API and Ternary Mixture

The Differential Scanning Calorimetry (DSC) thermograph of the nifedipine API, shown in figure 10, resulted that there was a single sharp endothermic peak at 176.68°C with an onset from 173.08°C and ending at 178.53°C. The crystalline nature of the drug as reported shows the endothermic peak between 175°C-180°C, as it melts between the said temperatures. The calculated parameters of the melting transition of the nifedipine are also presented in figure 10. The DSC thermogram of the ternary mixture of the nifedipine, represented in figure 11, hardly produces a trend of reduced melting temperature (Tm) of the characteristic endothermic peak of nifedipine. The disappearance of the sharp characteristics peak indicates the transition of the crystalline form of the nifedipine to the amorphous form. Further appearance of the broader peak at almost 70°C indicates formation of mesophage. This suggests that drug has been molecularly dispersed in the carrier.

This is further proved fact that the solubility and dissolution rate is greater in the amorphous form of the drug than crystalline. Thus the thermogram of the ternary mixture formed, due to the absence of characteristic peak, reveals the conversion of the nifedipine from crystalline form to the amorphous form.

Formation of powder blend

The powder blend was formed for tabletting of the ternary mixture in sufficient quantity.

Evaluation of powder blend prepared

The overall micromeritic characterization viz. angle of repose, bulk density, tapped density, hausner ration and carr's index, were obtained in acceptable range and compiled in table 5.

The powder blend now may be forward for tabletting as the parameters obtained are favourable for flow and compression of the powder blend into tablet.

Tablet Formulation and Evaluation

Tablet Formulation

The ternary mixture for nifedipine was weighed for equivalent quantity of nifedipine to 5mg. Tablet of weight 250mg was compressed. Weight of ingredients equivalent to twenty five tablets were weighed to prepare twenty tablets.

Tablet Evaluation

Following pharmacopoeial and non pharmacopoeial tests were performed for the 250mg tablet of nifedipine prepared from ternary mixture and shown in table 6.

General Appearance: The appearance of the tablet, its identity & elegance is essential for

consumer acceptance. The appearance of the tablet was round flat faced and yellowish colour.

Size and Shape: The size and shape of the tablet can be dimensionally described, monitored and controlled[39]. The diameter was 8mm and round shaped tablet was prepared

Weight Variation: Twenty tablets were used for weight variation test as per IP 2007. Each tablet was weighed on the analytical balance and weight was recorded. Percent deviation from the average weight was estimated[9][32][39]. All tablet formulations passed the weight variation tests as per Indian Pharmacopoeia (I.P.) 1996.

Tablet Crushing Strength /Hardness Test: The crushing strength of the tablets was measured with Pfizer Hardness tester which applies compression force diametrically to the tablets. The force required to crush the tablet was recorded as hardness in Kg[32][39]. Hardness was within the standard limits.

Friability Test: This test is intended to determine the physical strength of tablets during shipping and packaging stress**.** Tablets are brushed to remove excess powder prior to their initial weight determination and after 100 revolutions (25 revolutions per minute for four minutes). Ten tablets were used for friability test. The weights of tablets were compared before and after 4 min test (100 rotations)[9]. The friability for tablets was less than 1% as required by I.P.

Thickness: Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Digital Vernier Calipers. It was determined by checking twenty tablets from formulation[32][39]. The average thickness was 3.513mm with standard deviation of ±0.039. The diameter of the tablet was 8mm as the die and punches were of the similar size.

Disintegration Test: Six tablets were used for the disintegration test. Each tablet was kept in different tube of the disintegration test apparatus and discs were kept inside the tubes. The disintegration medium used was hydrochloric acid buffer pH 1.2. at 37±2°C[9]. All the tablets disintegrated quickly due to presence of large amount of crosscarmellose in the ternary mixture.

Drug Content: The drug content in the tablet was determined in triplicate.

In Vitro Release Studies: The drug release from the tablets were evaluated by carrying out *in vitro* dissolution studies[12][34][35][32]. The average drug release 93.63percent within 60min as mentioned in table 7 and figure 12.

Evaluation of Release Kinetics of Tablet

Model independent parameters: When dissolution data was subjected to model independent parameters, tablet prepared by ternary mixture of SD8 (optimized formulation) from conventional marketed tablet showed greater Mean Dissolution Time (MDT) and Percentage Dissolution Efficiency {%DE} within 60min as shown in table 8.

Model dependent parameters: In order to obtained meaningful information for release models, the drug release profiles were fitted to various kinetic models. Table 9 summarized the correlation coefficient for different release kinetic models of nifedipine optimized tablet and marketed formulation. Models with higher correlation coefficient were judged to be more appropriate model for dissolution data.

Model dependent parameters showed that correlation coefficient of optimized formulation was maximum for peppas order release kinetics compared to marketed tablet formulation.

Stability Studies

The tablets were packed in aluminum foil and kept in the equipment for three month at 40±2°C and 75±5%Relative Humidity (RH). One set of tablet was kept at room temperature (RT) at the same time.

Evaluation after stability study

Physical Appearance: The tablets were examined for physical appearance. The physical appearance of the tablets was not affected during and after the studies.

Dissolution Test: Three tablets were taken from the humidity cum stability chamber after three months and in vitro release studied. The cumulative % release obtained was 90.33percent with standard deviation of ±0.724 as reported in table 10.

Dissolution profile comparison by determination of similarity factor f2 for product kept at stress condition and normal conditions: There was no significant variation in the in vitro drug release profile over a period of three months. The similarity factor (f2 value) was found 51.65 which is more than 50 indicates similarity between both the dissolution profiles. Thus the results of the stability studies confirmed that the developed formulation is stable.

CONCLUSION

It can be concluded that the physical mixture, solid dispersion of nifedipine can be prepared with sodium starch glycollate, croscarmellose sodium, Eudragit E-100. The solid dispersions prepared can further be converted into ternary mixture and formulated in tablet dosage form. The model drug, nifedipine, with croscarmellose sodium in 1:7 ratio have excellent solubility and dissolution rate from the formulations. The ternary mixture with addition of certain excipients can further compressed into tablet dosage form and the tablet by compression of the ternary mixture with excipients has almost similar rate of drug release as the ternary mixture alone exhibit. The tablet dosage thus formed with the ternary mixture containing crosscarmellose sodium and neusilin US2 have greater solubility and dissolution rate comparatively to the existing marketed product.

ACKNOWLEDGMENT

The author is indebt with the Prof. Sanjeev Thacker, Principal, Seth G.L. Bihani S.D. College of Technical Education, Sri Ganganagar and management of the institute for kind cooperation and encouragement during the entire work. The author is further thankful to the suppliers of the ex-gratis samples, as cited, for their kind gesture.

Table 1: Formulation batches of nifedipine

S. No.	Method	Drug: Polymer Ratio	Formulation Code		
			With SSG	With CCM	With Eudragit E-100
1	Physical Mixture	1:1	PM1	PM5	PM9
2		1:3	PM2	PM6	PM10
3		1:5	PM3	PM7	PM11
4		1:7	PM4	PM8	PM12
5	Solid Dispersion	1:1	SD1	SD5	SD9
6		1:3	SD2	SD6	SD10
7		1:5	SD3	SD7	SD11
8		1:7	SD4	SD8	SD12

Table 2: Composition of tablet of nifedipine from ternary mixture

Ingredients	Amount (mg)	Amount (%)
Ternary mix (Equivalent to 5mg of Nifedipine)	80	32
Lactose Monohydrate	130	52
Micro Crystalline Cellulose	35	14
Talc	2.5	1
Magnesium Stearate	2.5	1
Total Weight	250	100

Table 3: Comparative cumulative % release of nifedipine API, marketed product (MP), physical mixtures and solid dispersions

Formulations / Time (min)	Cumulative % Release					
	5	10	15	30	45	60
Nifedipine API	33.45	38.27	44.51	47.70	50.24	52.45
Nifedipine MP	35.86	45.19	58.05	61.72	72.33	75.10
PM1	32.76	35.50	45.51	49.40	51.61	53.83
PM2	33.79	35.86	46.21	50.80	54.06	55.96
PM3	33.45	36.54	47.59	52.89	54.79	57.73
PM4	33.10	36.19	46.55	53.91	55.12	58.07
PM5	34.14	37.24	45.54	52.88	55.47	58.77
PM6	35.86	40.01	46.27	53.28	56.21	59.86
PM7	35.52	41.39	46.63	54.67	57.62	62.32
PM8	39.66	43.16	48.41	57.16	61.17	65.21
PM9	33.45	35.16	46.20	51.48	54.06	56.30
PM10	32.41	36.19	46.20	51.14	55.09	59.07
PM11	34.14	36.20	47.25	52.54	56.16	61.19
PM12	35.17	39.66	45.68	52.23	59.29	64.35

SD1	40.34	51.09	56.43	61.81	65.17	69.94
SD2	39.31	50.74	55.72	62.13	66.19	70.97
SD3	38.28	48.66	55.00	63.48	65.82	71.63
SD4	40.34	49.02	57.10	65.59	70.02	74.15
SD5	40.00	47.30	56.39	64.53	67.92	72.37
SD6	41.38	50.07	61.26	69.44	72.54	77.38
SD7	41.03	49.38	62.28	69.10	73.22	77.73
SD8	42.07	54.21	65.44	72.29	77.48	81.68
SD9	38.97	49.70	55.37	60.05	64.08	70.22
SD10	40.34	48.68	57.44	64.21	71.04	74.15
SD11	41.38	50.41	59.53	65.29	70.76	75.24
SD12	42.07	51.11	61.27	67.39	71.84	77.37

Table 4: Cumulative % Release of nifedipine from ternary mixture

S. No.	Time (min)	Cumulative % Release			Average	Standard Deviation (SD)	Relative Standard Deviation (%RSD)
		First Batch	Second Batch	Third Batch			
1	5	44.14	40.34	41.72	42.07	±1.92	4.56
2	10	56.65	59.02	57.31	57.66	±1.23	2.13
3	15	71.69	72.02	73.40	72.37	±0.91	1.25
4	30	76.54	81.01	79.99	79.18	±2.34	2.96
5	45	80.04	84.56	85.60	83.40	±2.95	3.54
6	60	91.51	95.38	96.43	94.44	±2.59	2.74

Table 5: Compiled micromeritic properties of powder blend

S. No.	Parameter	Average Value	Standard Deviation
1	Angle of Repose	23.946	±1.161
2	Bulk Density	0.753	±0.027
3	Tapped Density	0.886	±0.037
4	Hausner Ratio	1.177	±0.007
5	Carr's Index	15.055	±0.531

Table 6: Evaluation of tablet from optimized formulation

Weight Variation (mg)	Hardness (Kg.)	Friability (%)	Thickness (mm)	Disintegration Time (min.)	Drug Content (%)
249.69±1.728	3.87±0.24	0.76%	3.513±0.039	6.74±0.25	98.60±0.62

Table 7: Average cumulative percentage release of nifedipine from the tablet

S. No.	Time (min)	Cumulative % Release			Average	Standard Deviation (SD)	Relative Standard Deviation (%RSD)
		First Batch	Second Batch	Third Batch			
1	5	41.379	40.690	43.448	41.839	±1.436	3.431
2	10	56.621	57.648	59.055	57.775	±1.222	2.115
3	15	71.321	71.669	72.745	71.911	±0.742	1.032
4	30	80.300	77.548	79.669	79.172	±1.441	1.821
5	45	83.155	82.790	84.586	83.510	±0.949	1.137
6	60	92.238	92.903	95.752	93.631	±1.866	1.993

Table 8: Model independent parameters of optimized and marketed tablet

S.No.	Formulations	$\%DE_{(60min)}$	MDT
1	Optimized Tablet formulation	0.07	13.94
2	Marketed Tablet	0.06	12.43

Table 9: Model dependent parameters of optimized and marketed tablet

S. No.	Formulations	Evaluation parameters	Zero order	First order	Matrix model	Peppas model	Hixson-crowell model
1	Tablet of optimized formulation	R	0.3457	0.3462	0.9171	**0.9786**	0.3460
		K	0.0019	0.000	0.0135	**0.0279**	0.000
		n				**0.2964**	
2	Marketed tablet	R	0.3649	0.3653	0.9222	**0.9674**	0.3652
		K	0.0016	0.0000	0.0111	**0.0238**	0.000
		n				**0.2864**	

Table 10: Average cumulative percentage release of nifedipine from tablets at stresses conditions

S. No.	Time (min)	Cumulative % Release			Average	Standard Deviation (SD)	Relative Standard Deviation (%RSD)
		First Tablet	Second Tablet	Third Tablet			
1	5	38.966	40.000	39.310	39.425	±0.527	1.335
2	10	55.545	56.952	57.634	56.710	±1.066	1.879
3	15	70.924	69.931	69.586	70.147	±0.695	0.990
4	30	78.866	78.552	77.859	78.425	±0.515	0.657
5	45	82.397	81.734	82.069	82.067	±0.331	0.403
6	60	90.093	91.148	89.762	90.334	±0.724	0.801

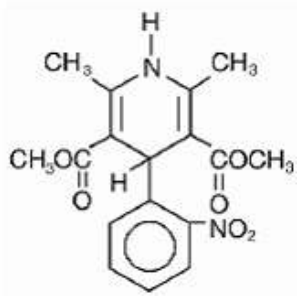

Figure 1: Chemical Structure of Nifedipine

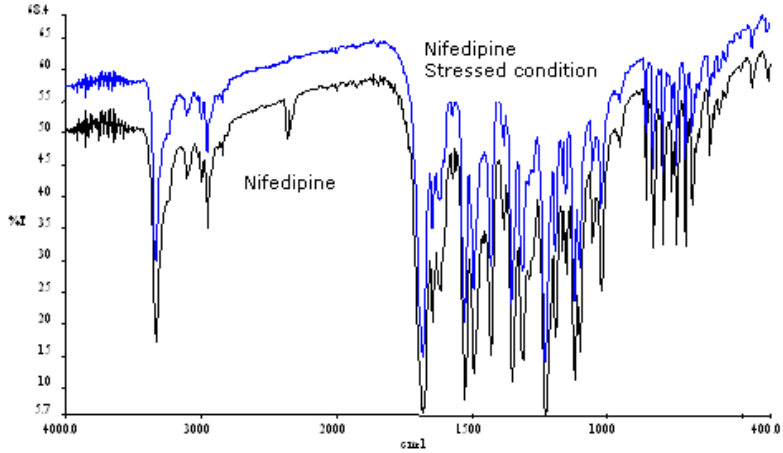

Figure 2: Comparative FT-IR of Nifedipine immediate and 30 days storage at 50°C

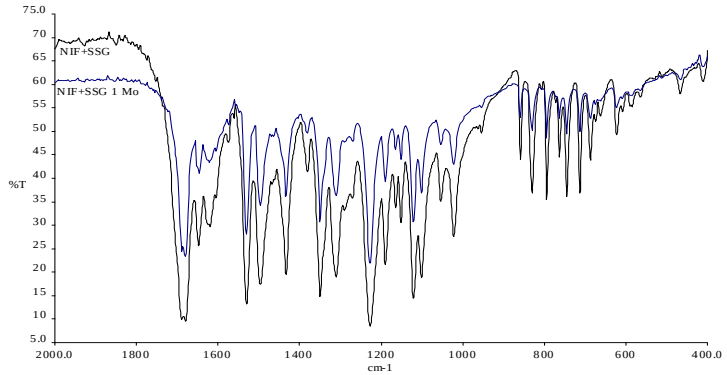

Figure 3: Comparative FT-IR of Nifedipine and Sodium Starch Glycollate immediate and 30 days storage at 50°C

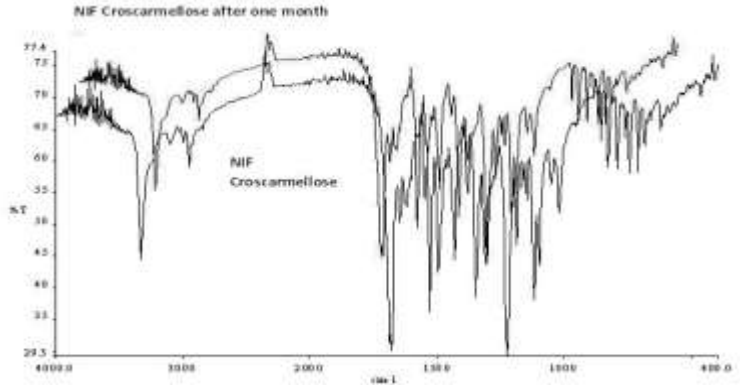

Figure 4: Comparative FT-IR of Nifedipine and Croscarmellose sodium immediate and 30 days storage at 50°C

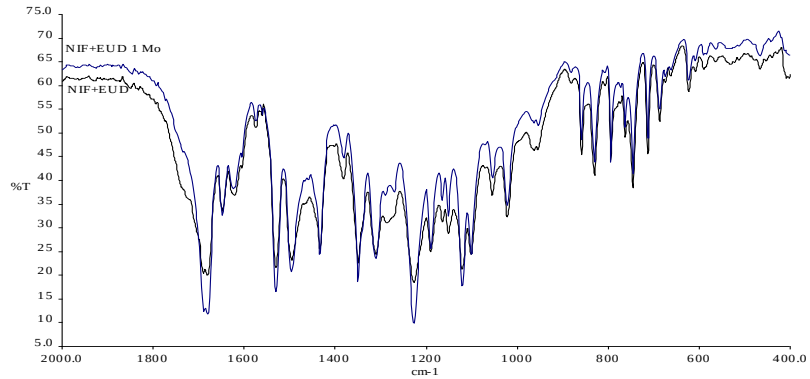

Figure 5: Comparative FT-IR of Nifedipine and Eudragit E 100 immediate and 30 days storage at 50°C

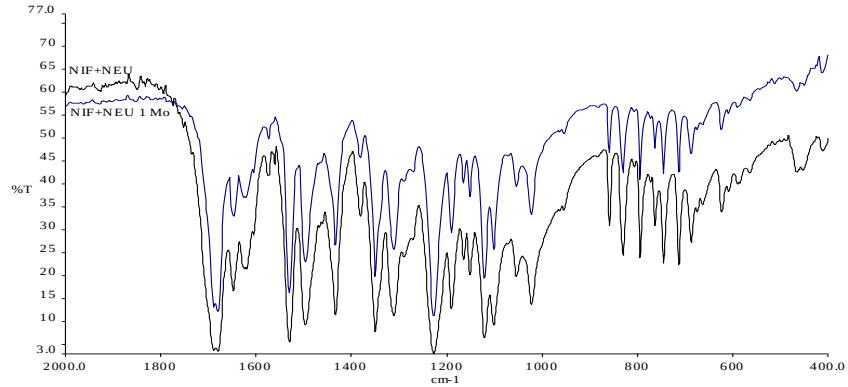

Figure 6: Comparative FT-IR of Nifedipine and Neusilin US2 immediate and 30 days storage at 50°C

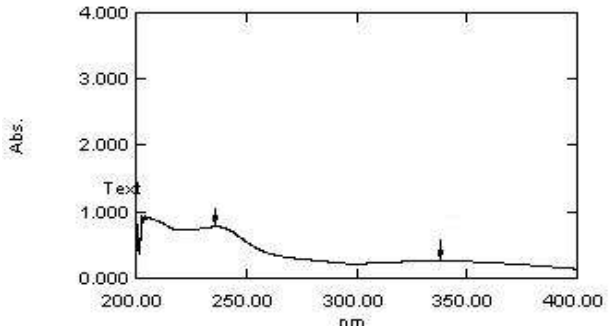

Figure 7: Nifedipine UV scan in hydrochloric acid buffer pH 1.2

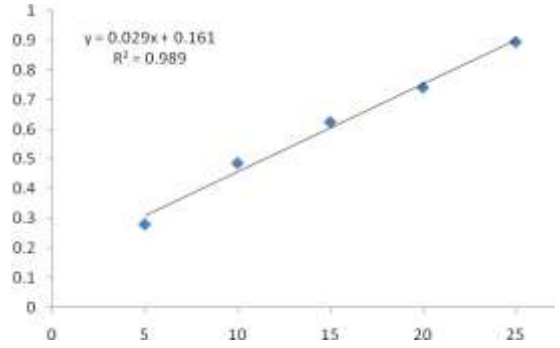

Figure 8: Nifedipine standard calibration curve in hydrochloric acid buffer pH 1.2 at λmax 236nm

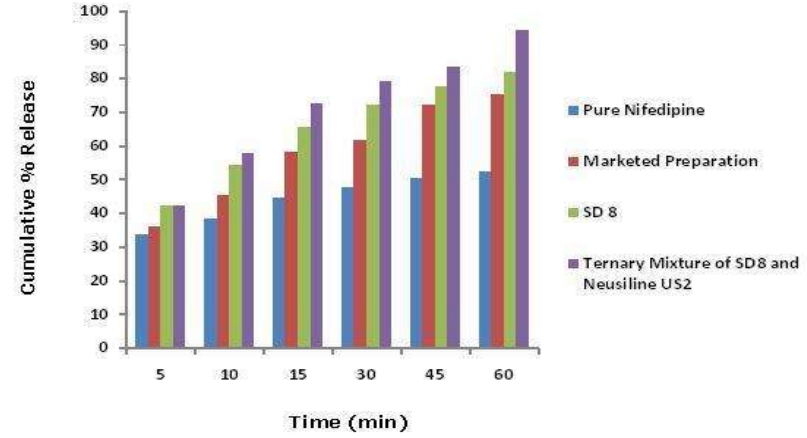

Figure 9: Dissolution profile of formulation Ternary mixture and its comparison to pure nifedipine API, marketed product and SD8

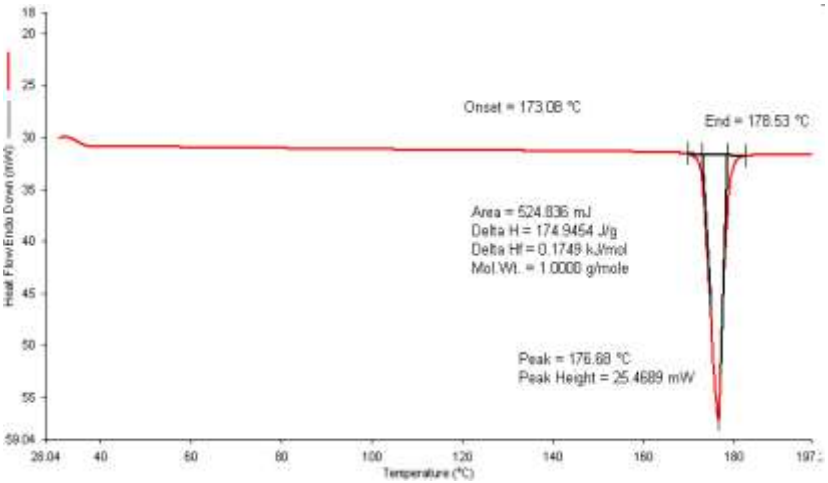

Figure 10: DSC Thermogram of Nifedipine API

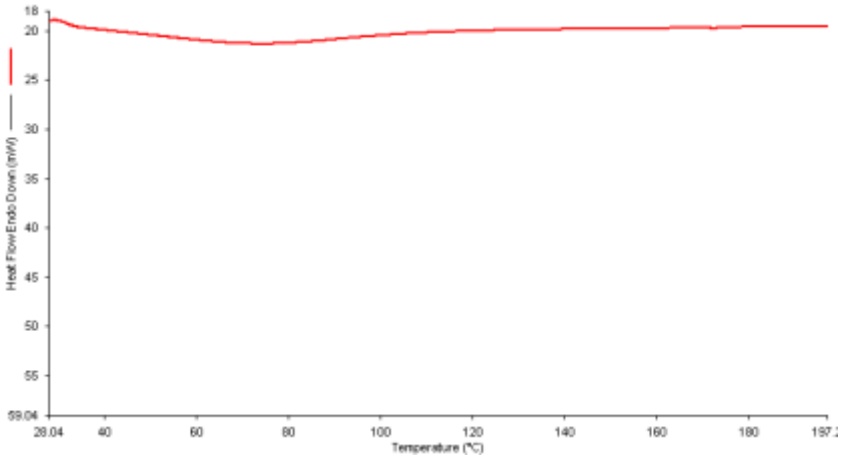

Figure 11: DSC Thermogram of Nifedipine Ternary Mixture

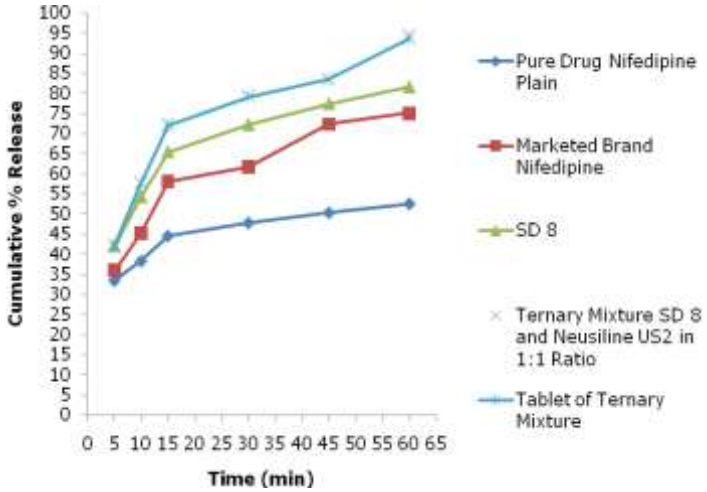

Figure 12: Dissolution profile of nifedipine tablet formulated, ternary mixture and its comparison to pure nifedipine API, marketed product and SD8

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