

DRUG-EXCIPIENTS COMPATIBILITY STUDIES OF NICORANDIL IN CONTROLLED RELEASE FLOATING TABLET

ABDUL BAQUEE AHMED*, LILA KANTA NATH

Girijananda Chowdhury Institute of Pharmaceutical Sciences, Hathkhowapara, Azara, Guwahati, Assam, India, Department of Pharmaceutical Sciences, Dibrugarh University, Dibrugarh, Assam, India. Email: baquee1977@gmail.com

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ABSTRACT

Objective: The present study was undertaken to assess the compatibility of Nicorandil with a number of commonly used tablet excipients to develop a controlled release floating tablet for Nicorandil.

Methods: Differential scanning Calorimetry (DSC), Isothermal stress testing (IST) and with the support of Fourier transform infrared spectroscopy (FT-IR) were used to evaluate compatibility of drug-exciipients mixture. The optimized formulation developed using the compatible excipients were evaluated for 3 months of stability studies at 2-8°C and 25°C/60% RH.

Results: The results of DSC, IST and FT-IR studies confirmed the absence of incompatibility of Nicorandil with the excipients used in the formulations. The result of stability studies shows that the formulations were more stable at refrigerator (2-8°C) than stored at 25°C/60%RH.

Conclusion: Overall, study concludes no concrete evidence of interaction between Nicorandil and the excipients used in formulation. Besides, the selection of proper excipients storage condition will also plays an important role in development of stable dosage form for Nicorandil.

Keywords: Nicorandil, Differential Scanning Calorimetry, Isothermal stress testing, Sustain release, Incompatibility.

INTRODUCTION

Nicorandil, N-[2-(Nitrooxy) ethyl]-3-pyridinecarboxamide (Figure 1), is used in the treatment of hypertension and angina pectoris. It is a potassium-channel opener providing vasodilatation of arterioles and large coronary arteries. Its nitrate component produces venous vasodilatation [1]. Nicorandil is a white crystalline powder with a faint characteristic odour; its molecular weight is 211.2 and pKa value, 3.18. It is freely soluble in water and has an elimination half-life of 1h, the therapeutic dose is in the range of 5–40 mg taken twice daily [2], and the drug is well absorbed from the small intestine. Successful treatment of cardiovascular diseases means maintenance of blood pressure at a normal physiological level, for which a constant and uniform supply of drug is, desired [3]. The constant and uniform supply of drug in blood can be achieved by designing an oral sustained release dosage form with improved gastric retention to facilitate complete absorption of released drug from the delivery system in gastrointestinal tract (stomach or small intestine).

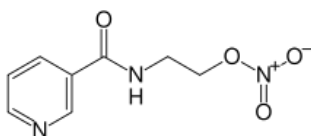


Fig. 1: Structural formula of Nicorandil

The successful formulation of a stable and effective solid dosage form depends on careful selection of the excipients. Most drugs intended for oral administration requires formulation with excipients to allow adequate administration, to facilitate the manufacture of the product, to increase the stability of the formulation, for aesthetic reasons or for identification. Although excipients traditionally have been thought of as being inert, excipients have shown that they can interact with the drug, preventing its absorption and bioavailability [4-5].

Drug-exciipient interaction is an important exercise in the development of a stable dosage form [6]. Despite the importance of drug-exciipients compatibility testing, there is no universally accepted protocol for this purpose. Differential scanning Calorimetry (DSC) has been extensively reported in the literature for testing compatibility of excipients with number of drugs [5, 7-11]. Another method that is commonly employed for evaluating the drug-

exciipients compatibility is Isothermal stress testing (IST). The method involves storing the drug-exciipients blends with or without moisture at high temperature and determining the drug content [9, 12-13]. DSC can be used in combination with IST to evaluate compatibility of drugs with the selected excipients.

In present study, techniques of DSC, IST and support of Fourier transform infrared spectroscopy (FT-IR) were used to assess the compatibility of Nicorandil with selected excipients as a part of preformulation testing for the development of controlled release floating tablet of Nicorandil. Exciipients found to be compatible were used for different formulation trials. Finally, the optimized formulation developed using the compatible excipients were evaluated for 3 months of stability studies at 2-8°C and 25°C/60% RH.

MATERIALS AND METHODS

Materials

Nicorandil was a gift sample from Torrent Pharmaceutical Ltd. Baddi, India. HPMC K100M was received as gift samples from Colorcon Asia Pvt Ltd. Goa, India. Spray dried lactose was purchased from Meggle GmbH, Wasserburg, Germany.

Aerosil 200 and Eudragits RSPO were collected from Degussa, Germany. Sodium bicarbonate, Loba Chemie Pvt. Ltd., Mumbai, India; and all other ingredients were procured from the local supplier and were of analytical grade.

Differential scanning Calorimetry

A differential scanning calorimeter (Jade DSC, Perkin Elmer, USA) was used for thermal analysis of Nicorandil and Nicorandil-exciipients mixtures. Individual samples (Nicorandil and excipients) as well as physical mixtures of Nicorandil and selected excipients (all passed through 60-mesh sieve) were weighed directly in the pierced DSC aluminium pan (Table 1) and scanned in the temperature range of 20–300°C under an atmosphere of dry nitrogen. Heating rate of 10°C/min was used and thermograms obtained were observed for any interaction

FT-IR spectroscopy

FT-IR spectra were recorded on a Bruker spectrophotometer (Model-220, Germany) using KBr discs in the range of 4000–400 cm⁻¹. FT-IR analysis has been performed using sample of Nicorandil with various excipients at 1:1 mass/mass ratio

Table 1: Peak temperature and enthalpy values of Nicorandil in various drug–excipients mixtures

Sample	Ratio (drug-excipients)	$T_{peak}(^{\circ}C)$	$\Delta H_{f\ corr}$ (J/g) ^a
Nicorandil	-----	97.50	91.34
Nicorandil + Spray dried lactose	1:3	101.73	85.23
Nicorandil + NaHCO ₃	1:1	100.99	83.24
Nicorandil + Eudragits RSPO	1:1	93.63	89.21
Nicorandil + Aerosil200	1:1	97.12	73.24
Nicorandil + HPMC K100M	1:2	98.50	95.25

^a $H_{f\ corr} = \Delta H_{f\ obs}/\%drug\ in\ sample \times 100$; from reference [8].

Table 2: Results of analysis of IST samples after 3 weeks of storage at stressed conditions (stored at 50°C)

Sample	Ratio (drug-excipients)	% Remaining (\pm SD, n = 3)	
		Control conditions @ 2-8°C	Stressed conditions @ 50°C
Nicorandil	-----	101.12 \pm 0.11	96.74 \pm 0.06
Nicorandil + Spray dried lactose	1:3	102.50 \pm 0.21	97.23 \pm 0.11
Nicorandil + NaHCO ₃	1:1	99.92 \pm 0.09	97.24 \pm 0.13
Nicorandil + Eudragits RSPO	1:1	101.63 \pm 0.24	96.21 \pm 0.21
Nicorandil + Aerosil200	1:1	99.12 \pm 0.12	98.25 \pm 0.31
Nicorandil + HPMC K100M	1:2	101.50 \pm 0.18	96.25 \pm 0.11

Isothermal stress testing

For IST studies, Nicorandil and different excipients (Table 2) were weighed directly in 4ml glass vials ($n=3$) and mixed on a vortex mixer for 2 min. In each of the vials, 10% w/w water was added and the Nicorandil–excipients blend was further mixed with a glass capillary (both the ends of which were heat sealed).

To prevent any loss of material, capillary was broken and left inside the vial. Each vial was sealed using a Teflon-lined screw cap and stored at 50°C. These samples were periodically examined for any unusual colour change. After 3 weeks of storage at the above conditions, samples were quantitatively analyzed using UV spectrophotometer (UV- 1800-Double beam spectrophotometer, Shimadzu, Japan).

Nicorandil–excipients blends without added water and stored in refrigerator (2-8°C) served as control

Formulation development and stability studies

Floating tablet of Nicorandil was prepared by passing Nicorandil, HPMC K100M and Eudragits RSPO through sieve No. 80 separately. The drug was mixed with the polymers and other ingredients in weight proportion as mentioned in Table 3. The powder blend was then lubricated with Aerosil 200 (2% wt/wt), and this lubricated blend was compressed into tablets using 9 mm flat-face 8 station tablet punching machine (Shakti, Ahmadabad, India).

The compression force was adjusted to obtain tablets with hardness range of 5 to 6 kg/cm².

Table 3: Composition of optimized floating tablets of Nicorandil

Ingredients	% w/w
Nicorandil	13.34
HPMC K100M	33.34
Eudragits RSPO	6.66
Spray dried lactose	24.66
NaHCO ₃	20.00
Aerosil200	2.00

Total weight of tablet = 300 mg

In stability testing, the optimized formulation of Nicorandil was packed in strips of 0.04 mm thick aluminum foil laminated with PVC coating and stored in stability chambers (REMI, Environmental Test Chamber, Vasai, India) maintained at 25°C/60% RH and refrigerator (2-8°C). The samples were withdrawn periodically and subjected to assay, *in-vitro* buoyancy test and dissolution studies.

For assay, one accurately weighed tablet ($n=5$) was dissolved in 100 ml of distilled water. The samples were sonicated (Ultra sonic water bath, 3510, Branson, USA) for 30 min, the solution was filtered through a cellulose acetate membrane filter (0.45 μ m) and the drug content was determined by UV spectrophotometer (UV-1800 Double beam spectrophotometer, Shimadzu, Japan) at a wavelength of 262 nm after a suitable dilution.

The *in vitro* buoyancy was determined by measuring floating lag time, as per the method described by Rosa *et al.* 1994: [14]. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the time for which the

tablet constantly floats on the surface of the medium (duration of floating), was measured.

Dissolution testing of the formulations ($n=3$) was carried out using USP-II dissolution apparatus (Electro lab, India) at 100 rpm. Simulated Gastric Fluid, pH 1.2 (900 ml) maintained at 37 \pm 0.5°C was used as dissolution medium. The samples (5 ml) were withdrawn from the dissolution apparatus at the appropriate time intervals for 12 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 μ m membrane filter and diluted to a suitable dilution with Simulated Gastric Fluid, pH 1.2. Absorbance of these solutions was measured at 262 nm using a Shimadzu UV- 1800 spectrophotometer.

Assessment of difference factor and similarity factor

Release profiles of formulation stored at different storage conditions were compared using model independent pair-wise approach, which included the calculation of “difference factor”, f_1 and “similarity factor”, f_2 . These fit factors directly compare the difference between

the percent drug released for a reference and a test product [15]. The difference factor (f_1) measures the percent error between the two curves over all time points and is calculated as follows:

$$f_1 = \frac{\sum_{j=1}^n |R_j - T_j|}{\sum_{j=1}^n R_j} \times 100$$

Where n is the number of sampling points, R_j and T_j are the percent dissolved of the reference and test products at each time point j . The two release profiles are considered to be similar, if f_1 value is lower than 15 (between 0 and 15). The similarity factor (f_2) is a logarithmic transformation of the sum of squared error of differences between the test T_j and the reference products R_j over all time points. It was calculated using the following equation:

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \sum_{j=1}^n W_j |R_j - T_j|^2 \right)^{0.5} \right] \times 100 \right\}$$

The two dissolution profiles are considered to be similar, if f_2 value is more than 50 (between 50 and 100). For the calculation of f_1 and f_2 values, all data points of release study were taken into consideration.

RESULTS AND DISCUSSION

DSC scans of Nicorandil and Nicorandil–excipient mixtures are shown in Figures 2–7. The thermal behaviour of pure Nicorandil,

respective excipient, and the combination of Nicorandil and excipients is compared in the DSC thermograms. Peak transition temperature (T_{peak}) and heat of fusion or enthalpy (ΔH_f) of Nicorandil in various excipients mixtures is summarized in Table 1.

The DSC curve of Nicorandil showed a first endothermic event between 89 and 102°C (Figure 2) ($\Delta H_{fusion} = 91.34 \text{ J g}^{-1}$), with a melting temperature of ($T_{onset} = 97.58^\circ\text{C}$). These endothermic peak was also retained in all the mixture of drug–excipients with little shifting of the peaks which may be due to the presence of moisture or impurity of the excipient. The DSC scan of sodium bicarbonate showed a broad endothermic peak at 181.33°C (starting from 142.98 °C and ending at 216.76 °C), which may be attributed to the loss of adsorbed water.

The thermogram of Nicorandil–sodium bicarbonate mixture showed an endothermic peak of drug at 100.2°C, indicating that there was no interaction (Figure 3). The DSC scan of HPMC K100M showed a broad endothermic peak at 107.99°C (starting from 80.98°C and ending at 142.76°C), the thermogram of Nicorandil– HPMC K100M mixture showed an endothermic peak of drug at 98.23°C, indicating that there was no interaction (Figure 4). The DSC scan of spray dried lactose showed endothermic peaks at 158.74°C and 225.98°C, the thermogram of Nicorandil–spray dried lactose mixture showed an endothermic peak of drug at 97.35°C indicating the absence of chemical incompatibility between Nicorandil and spray dried lactose (Figure 5).

The endothermic peak of Nicorandil was found at 93.63°C and 97.12°C in the mixture of Nicorandil– Eudragits RSPO (Figure 6) and Nicorandil–Aerosil 200 (Figure 7) respectively indicating the absence of interaction

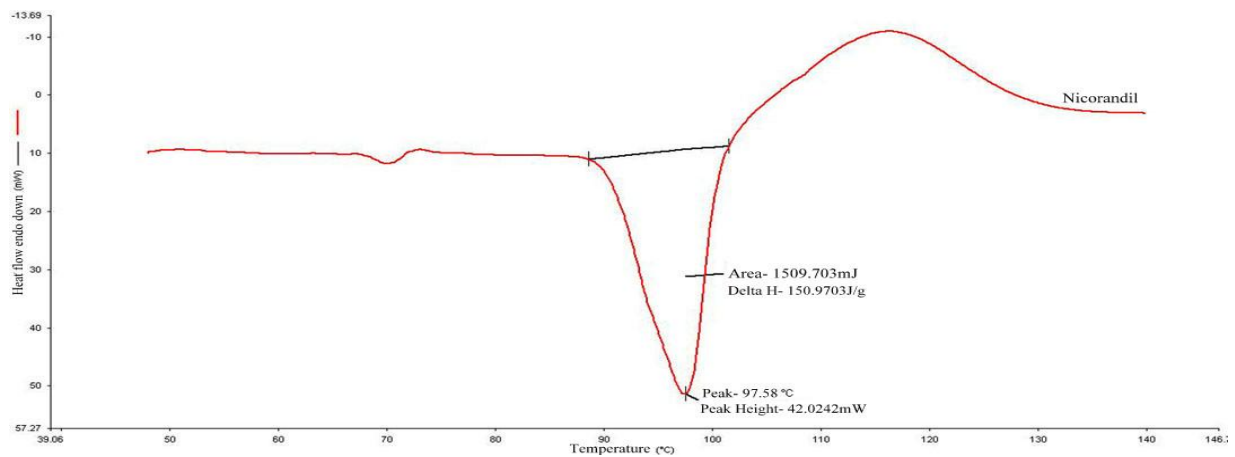


Fig. 2: DSC thermogram of Nicorandil

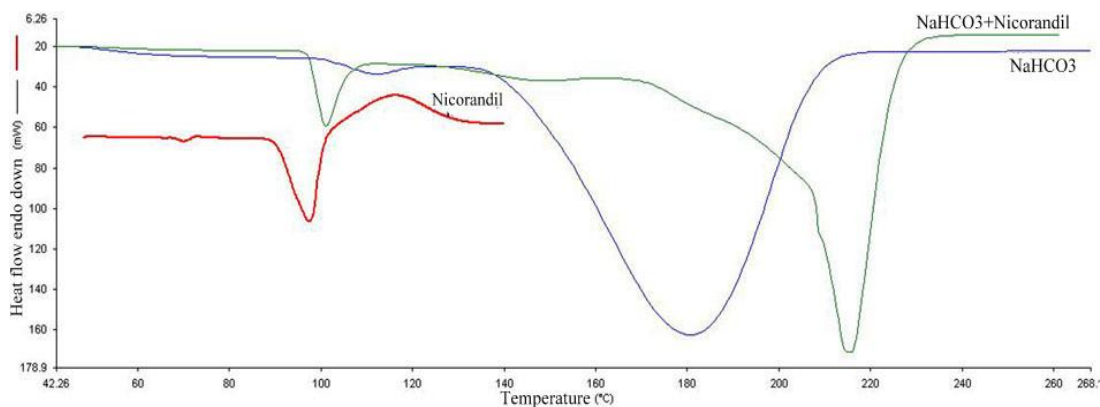


Fig. 3: DSC thermogram of Nicorandil with sodium bicarbonate

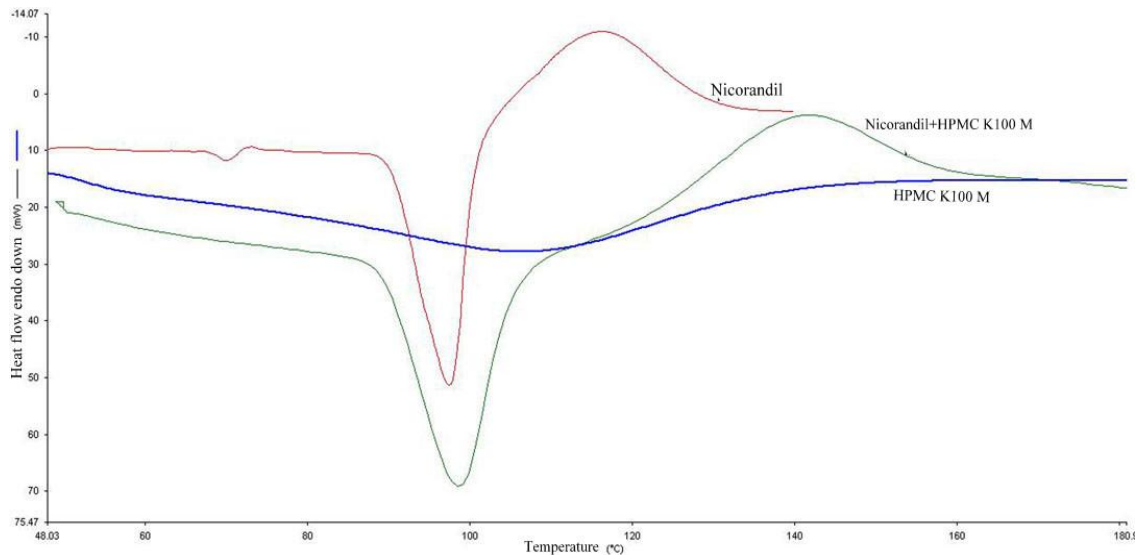


Fig. 4: DSC thermogram of Nicorandil with HPMC K100M

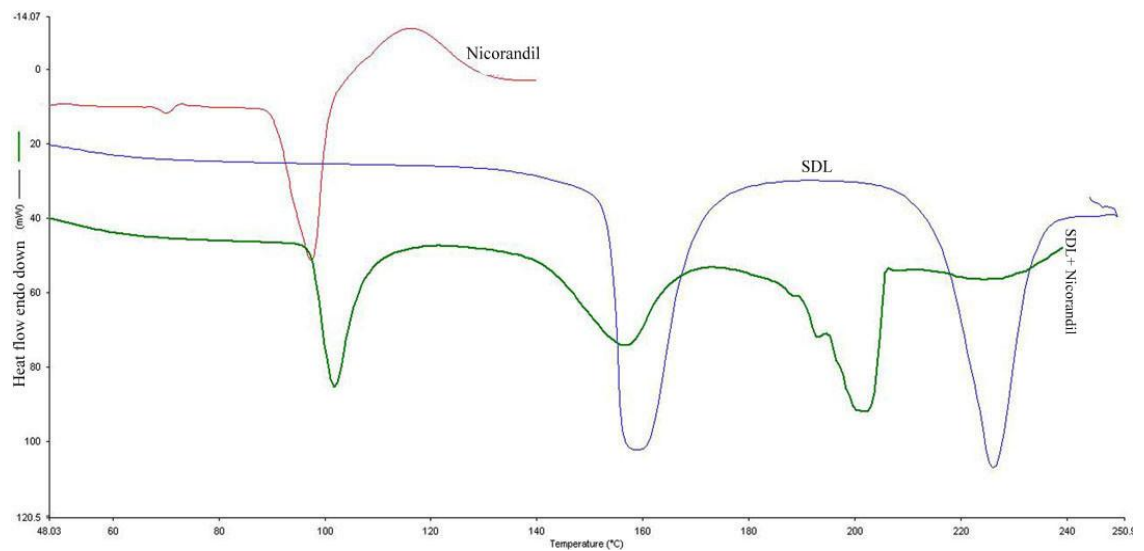


Fig. 5: DSC thermogram of Nicorandil with spray dried lactose

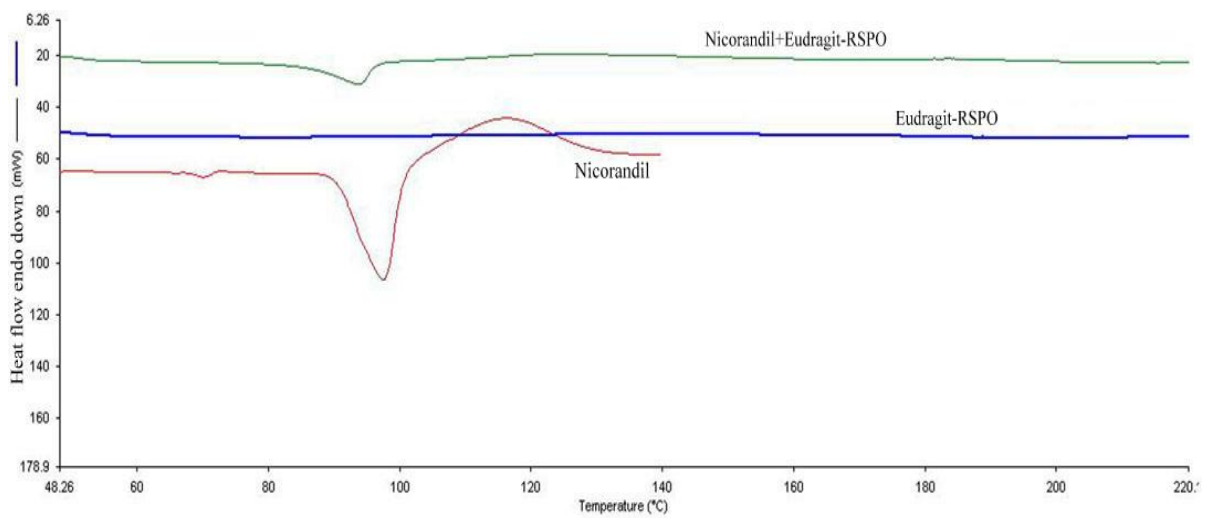


Fig. 6: DSC thermogram of Nicorandil with Eudragits RSPO

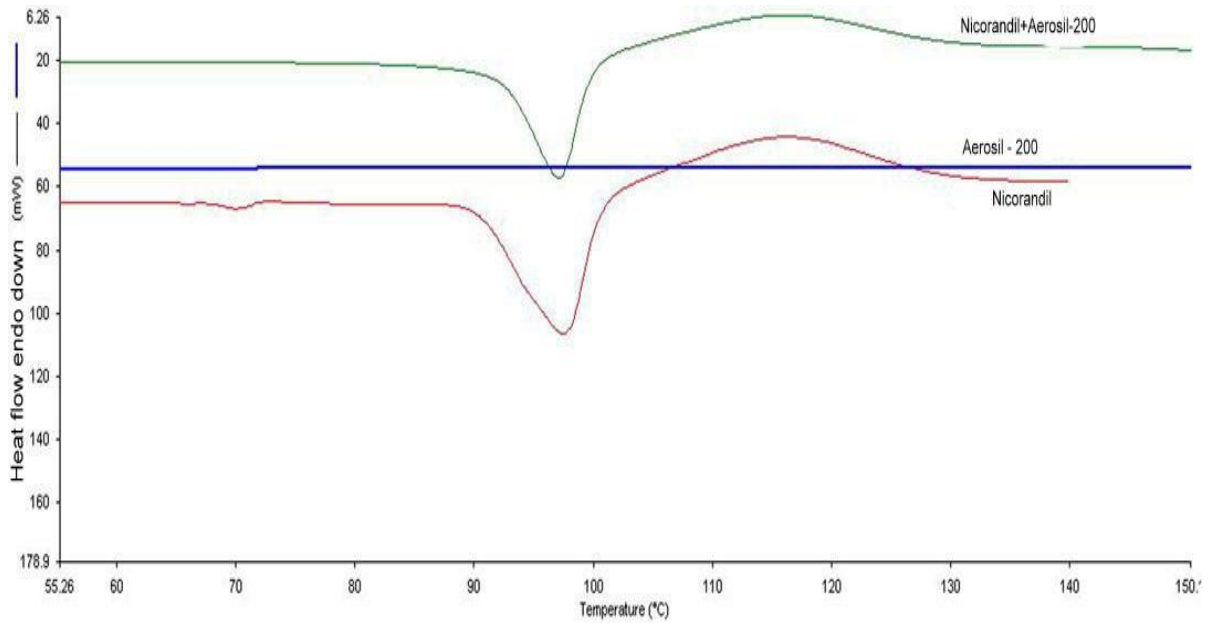


Fig. 7: DSC thermogram of Nicorandil with Aerosil200

In majority of the cases, melting endotherm of Nicorandil was well preserved with slight changes in terms of broadening or shifting towards the lower/higher temperature. It has been reported that the quantity of material used, especially in drug-excipient mixtures, affects the peak shape and enthalpy [9-10]. Thus, these minor changes in the melting endotherm of drug could be due to the mixing of drug and excipient, which lowers the purity of each component in the mixture and may not necessarily indicate potential incompatibility [11, 16-18]. The results of DSC studies were further correlated with FT-IR and IST results.

FT-IR spectrum of Nicorandil is shown in (Figure 8) and the following characteristics band were observed 3247cm^{-1} for (NH); 1675cm^{-1} for (C=O, CONH); 1362cm^{-1} for (CH_2) and 1590cm^{-1} for (Pyridinium ring). The above characteristics band for Nicorandil is also found in various Nicorandil-excipients mixture. FT-IR spectra of HPMC K100M and Nicorandil- HPMC K100M were shown in Figure 9 and Figure 10 respectively. The comparative FT-IR spectra of Nicorandil, HPMC K100M and Nicorandil-HPMC K100M shown in Figure 11 indicating the absence of interaction

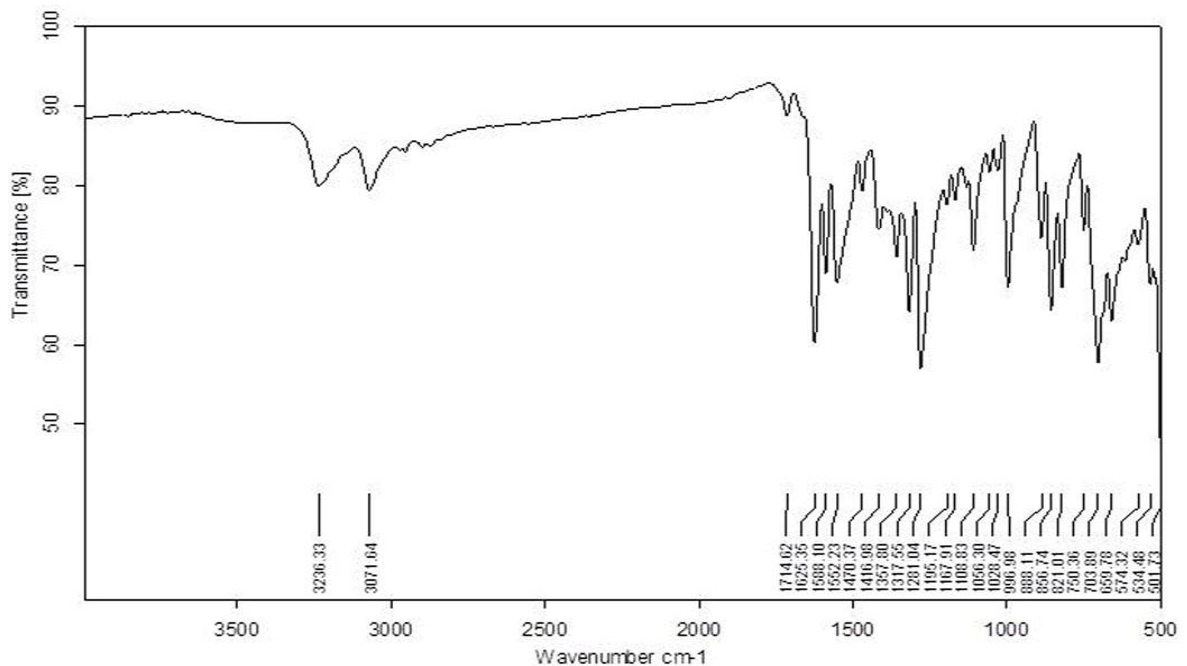


Fig. 8: FT-IR spectra of Nicorandil

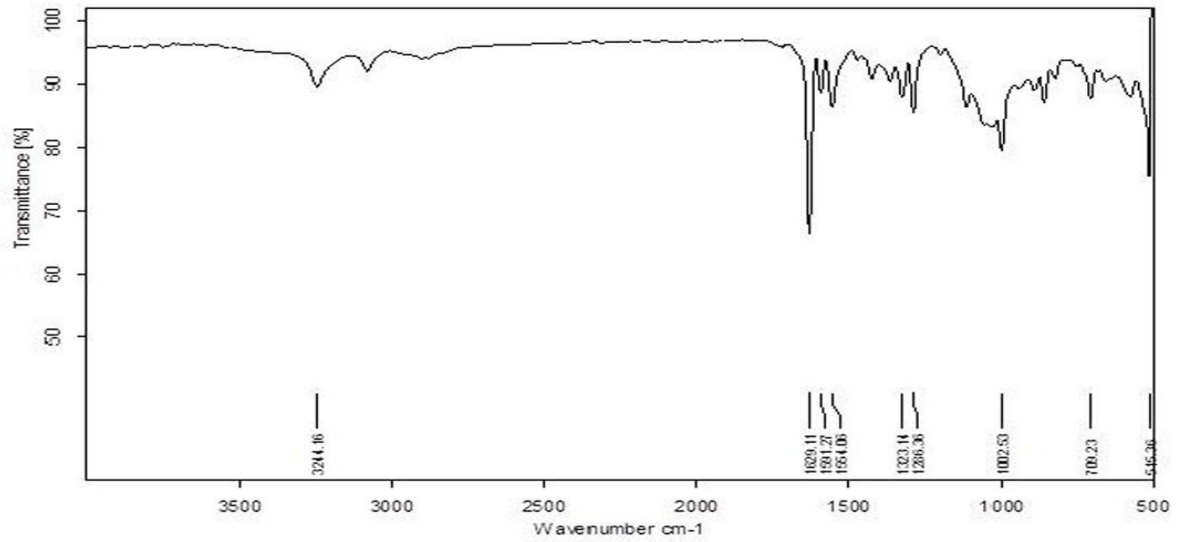


Fig. 9: FT-IR spectra of HPMC K100M

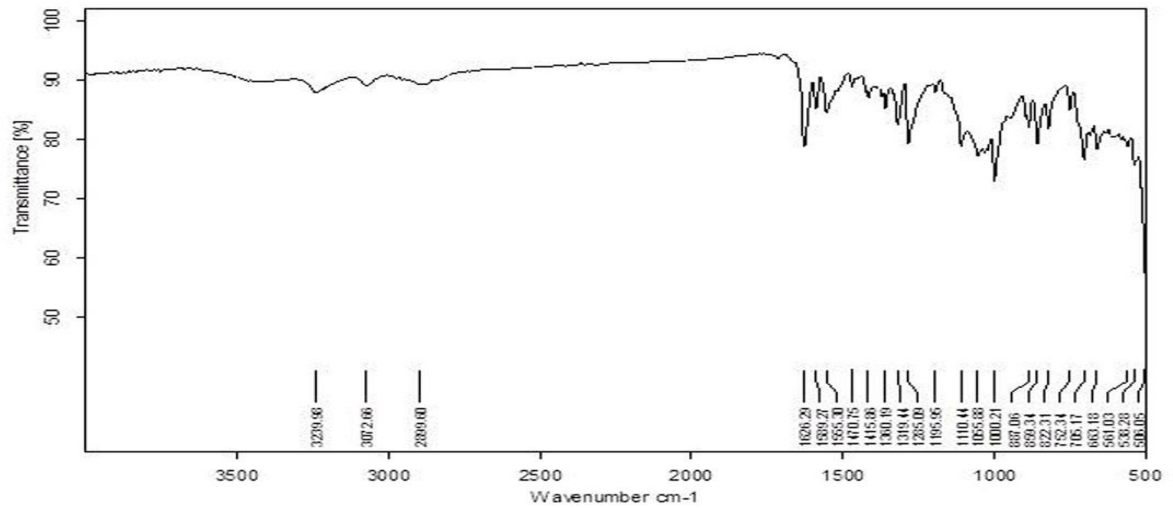


Fig. 10: FT-IR spectra of Nicorandil + HPMC K100M

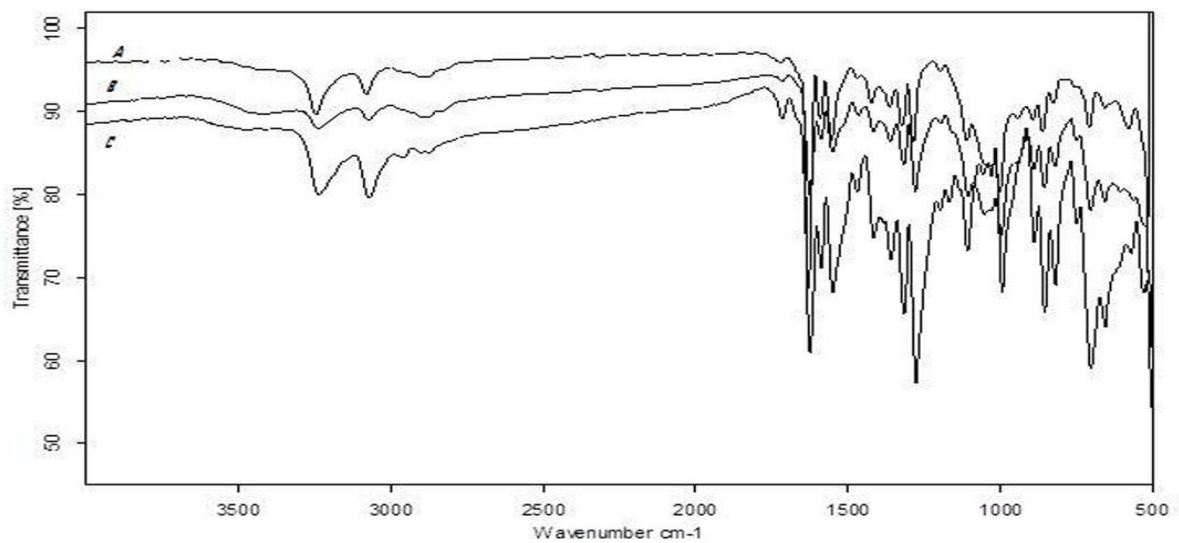


Fig. 11: FT-IR spectra of HPMC K100M (A), Nicorandil + HPMC K100M (B), Nicorandil (C)

Results of Isothermal Stress Testing (IST) studies showed in Table 2. The content of drug in all the Nicorandil-excipients mixtures were found in the range of $99.12 \pm 0.12\%$ to $102.50 \pm 0.21\%$ in controlled condition (Refrigerator, 2-8°C) and in stressed condition (stored at 50°C) was $96.21 \pm 0.21\%$ to $98.25 \pm 0.31\%$. The results showed 3-5% variations in stressed condition with respect to controlled condition and the difference in drug content in the mentioned conditions was found statistically significant $p=0.0032$ ($p<0.05$), indicating the decomposition of Nicorandil at stressed condition. This result was in agreement with the earlier studies performed by Dnyanesh and Pradeep, 2002, [19].

Thus, this result does not necessarily indicate the incompatibility of Nicorandil with the excipients used at the mentioned Nicorandil-excipients mixtures, because the DSC and FT-IR studies showed the presence of Nicorandil peak in all Nicorandil-excipient mixtures. The changes of drug content in the stressed condition may due to the thermodynamic instability of Nicorandil at 50°C.

Formulation development and stability studies

The optimized formulation showed hardness of 6.52 ± 0.17 Kg/cm², drug content of $102.13 \pm 0.12\%$, Floating lag time of 2.4 ± 0.02 min,

and drug release of $23.14 \pm 0.75\%$, $37.95 \pm 1.84\%$, $65.11 \pm 3.26\%$, $90.96 \pm 2.05\%$ at 2, 4, 8, 12 hours respectively.

The optimized formulation, packed in strips of 0.04 mm thick aluminium foil coated inside with polyethylene, was evaluated after 3 months of storage at stability conditions (25°C/60%RH) and at refrigerator (2-8°C) results of which are shown in Table 4 and Figure 12. It is evident that the formulation is having good stability in terms of both drug content and dissolution stability stored at refrigerator (2-8°C).

There was little change in the drug content (Table 4) after 3 month of storage at stability conditions (25°C/60%RH), but the change of drug content was not statistically significant as $p>0.10$ (Paired t test).

The floating lag time was found similar in both the storage conditions after 3 months of study. Release profile can be consider as similar after 3 months of stability studies as shown by the difference factor and similarity factor values $f_1=10.73$ (less than 15) and $f_2=51.49$ (more than 50) respectively. Based on the results, it can be concluded that the formulations are more stable storage at refrigerator (2-8°C) than the storage at 25°C/60%RH

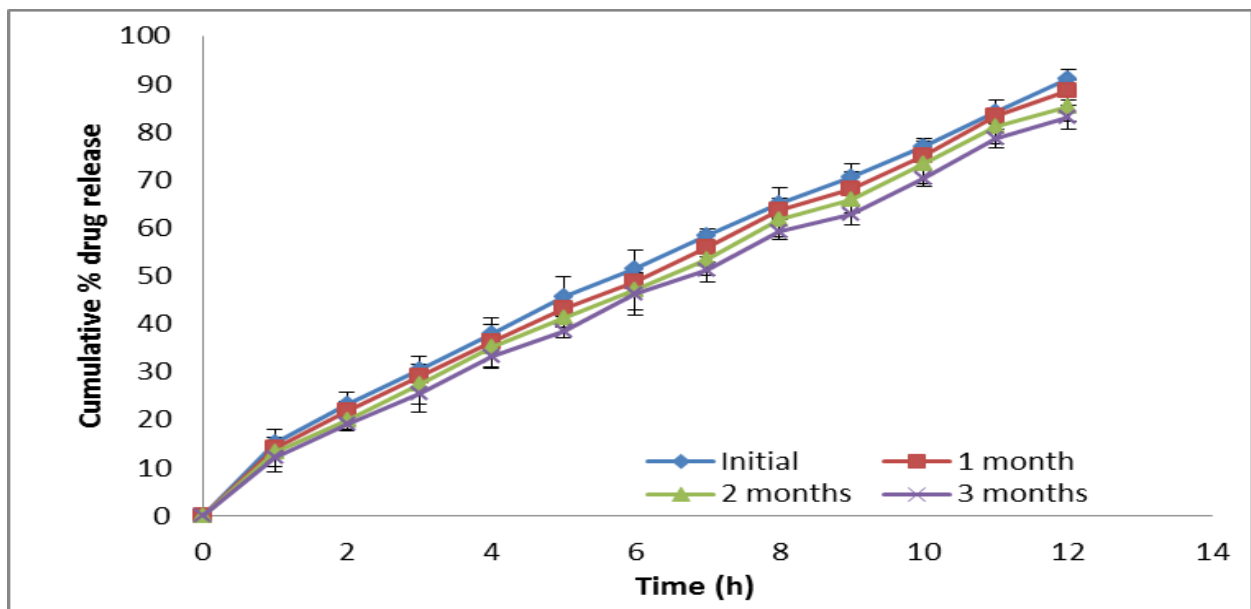


Fig. 12: Dissolution stability of optimized Nicorandil formulations after 3 months of storage @25°C/ 60% RH stability conditions

Table 4: Stability studies results of optimised formulation after 3 months of storage @25°C/ 60% RH and refrigerator @ 2-8°C.

Parameter	Refrigerator @ 2-8°C				Storage @ 25°C/60% RH		
	Initial	One month	Two months	Three months	One month	Two months	Three months
% Drug content (\pm SD, n = 5)	102.13 ± 0.12	101.87 ± 0.23	101.12 ± 0.02	101.53 ± 0.14	101.34 ± 0.12	100.78 ± 0.16	98.84 ± 0.23
Floating lag time(min) (\pm SD, n=5)	2.4 ± 0.02	2.5 ± 0.02	2.6 ± 0.03	2.4 ± 0.03	2.6 ± 0.03	2.7 ± 0.02	2.7 ± 0.03
f_1 value ^a	-----	-----	-----	-----	3.37	6.9	10.73
f_2 value ^a	-----	-----	-----	-----	75.03	60.72	51.49

^aInitial sample (0-month) of refrigerator @ 2-8°C condition was taken as reference to calculate f_1 and f_2 values.

CONCLUSIONS

Overall, this study concludes no concrete evidence of interaction between Nicorandil and all the excipients used in the development of floating tablet of Nicorandil. The result of DSC revealed absence of incompatibility indicating the presence of Nicorandil in all

Nicorandil-excipients mixtures with slight broadening and shifting of endothermic peaks with some excipients which may be due to the presence of moisture or physical interaction or impurities. Furthermore, to ruled out any interaction IST and FT-IR studies were conducted and the results of IST and FT-IR studies confirmed the compatibility of drug with the excipients used in the

formulations. The result of stability studies showed that the formulations were more stable storage at refrigerator (2-8°C) than stored at 25°C/60%RH. Thus, besides the selection of proper excipients storage condition will also plays an important role in development of stable dosage form for Nicorandil.

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