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PHOTOSTABILITY STUDIES OF NIFEDIPINE FOR PHOTOSTABLE COMPLEX IN DRUG DELIVERY SYSTEM

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ABSTRACT

The present research work was to improve the physiochemical stability of nifedipine by complexation using weak cation-exchange resins, indion 234 to eliminate light decomposition tendency of drug. Resinate were prepared by batch process using various drug-resin ratio (1:1, 1:2, 1:4). Irradiation test for drug degradation was carried out by comparing pure nifedipine drug, methanolic drug solution and resinates to determine differences in the effectiveness of artificial light and natural indirect sunlight sources. Further, resinates were subjected to different *in-vitro* evaluation tests for loading of drug in resin, FTIR and DSC studies for confirmation of complex and *in-vitro* drug release study. The batch process of complexing nifedipine with Indion 234 (1:2) produced efficient drug loading. The efficacy of fluorescent light as compared to the tungsten lamp was found to be slightly more than fluorescent light. The nifedipine was degraded rapidly in methanolic solution form, slowly in powder form and very slowly in resinate form. Indion 234 was found to be better complexing agent for reducing the photosensitivity and help to design stable nifedipine in drug delivery systems.

KEYWORDS: Nifedipine, Photostability, Ion-exchange resin, Indion 234.

INTRODUCTION

The photosensitive drugs undergo important chemical changes, accompanied by alteration in their activities and in some cases total loss of their therapeutic activity.[1] The certain drugs are very highly sensitive to photo oxidation such as nifedipine, montelukast etc. These drugs undergo changes in chemical, physical and therapeutic properties. Manufacturers of such products use light resistant coating or packing to minimize their photo degradation. Long term exposure to sunlight or artificial light may also occur if such formulations are improperly stored by patients. Poor storage conditions may potentially decrease clinical efficacy of photosensitive products.[2] So it becomes necessary to formulate photo stable formulations. The photodegradation takes place when absorption spectrum of drug matches with that of source or incident radiation.[3] The direct reaction occurs when these substances absorb light energy directly which will lead to intermediate products and these intermediates are converted to stable molecules by indirect reaction. The basic thing behind these reactions is to convert these substances into stable molecules (stable to light radiation which is absorbed by photolabile drug or pharmaceuticals). In indirect reactions or sensitizing reaction, the light energy may be absorbed by excipients, intermediates which further imparted to drug and leads to further degradation. The direct reaction does not depend on temperature for activation of the molecules while the intermediates in the indirect process can eventually react through 'dark' reaction to form the final, stable products. Various reactions which can take place in photochemical process include oxidation, hydrolysis, hydroxylation, isomerization, decarbonylation, decarboxylation, N-dealkylation etc. The chemical species which absorb light energy and undergo photodegradation include some important functional groups such as carbonyl group, carbon–carbon double bond, and C-H bond in alcohols amines sulphides may be involved in some photosensitization reactions. Among aromatics nitro group and among heterocyclic compounds five membered rings may lead to photosensitization. The rate of degradation of compounds depends on the concentration of these species present in molecule and also on concentration of solutions.[4]

Nifedipine, 1, 4-dihydro-2, 6-dimethyl-4- (2-nitrophenyl)-3, 5-pyridine dicarboxylic acid dimethyl ester is the prototype compound of the dihydropyridine class of calcium channel antagonists (figure 1). Nifedipine is a selective arterial dilator, and is used for the treatment of hypertension, angina pectoris, and other

cardiovascular disorders.[5] Nifedipine can undergo photodegradation accompanied by loss of pharmacological activity and even toxic products when they are irradiated by ultra-violet/visible lights. This process involves the reduction of the aromatic nitro group to nitroso group or the oxidation of the dihydropyridine ring to a pyridine ring.[5,6] For the safety of patient, it is important to note that the patient must have to receive a uniform dose of drug throughout the whole of the shelf life of product. Instability of a drug product may lead to decrease in bioavailability. The absorption spectrum of nifedipine in the long-wavelength region is between about 350 and 450 nm. Several studies related to its photodecomposition have been reported.[1]

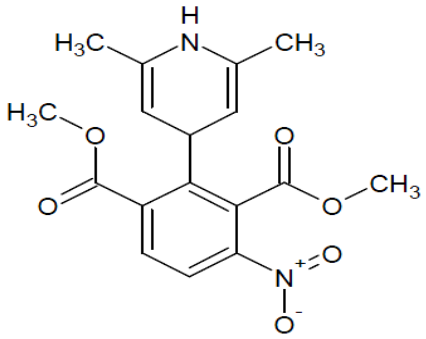

Fig. 1: Dimethyl 2, 6-dimethyl-4-(2-nitrophenyl)-1, 4 Dihydropyridine-3, 5-dicarboxylate.

Ion-exchange resins are solid and befittingly high relative molecular mass polyelectrolytes which will exchange their mobile ions of equal charge with close medium reversibly and stoichiometrically. Ion-exchange resins have versatile properties as drug delivery vehicles and have been extensively studied in the development of novel drug delivery systems.[7] An ion exchange resin is an insoluble matrix (or support structure) normally in the form of small (1-2 mm diameter) beads, usually white or yellowish, fabricated from an organic polymer substrate backbone.[7] The material has a highly developed structure of pores on the surfaces from where the ions are trapped or released. The trapping of ions takes place only with simultaneous release of other ions; thus, the process is called ion exchange.[8] These resins are being used extensively in overcoming various formulation-related problems including poor stability and poor dissolution, for taste masking and as a powder processing aid.[8-10] Drug molecules attached to resin are released by exchanging with appropriate charged ions in GIT, followed by diffusion of free drug molecule out of resins. The process can be depicted by following equations for anion and cation exchange resin respectively, where X and Y are ions in the GI tract.

$$Resin^{+}\text{-}Drug^{-} + X^{-} \rightarrow Resin^{+}\text{-}X^{-} + Drug^{-}$$
$$Resin^{-}\text{-}Drug^{+} + X^{+} \rightarrow Resin^{-}\text{-}X^{+} + Drug^{+}$$

Resins involve ion exchange as the reversible interchange of ions between solid and a liquid phase in which there is a no permanent change in the structure of solid. The solid is the ion exchange material while ion could be a drug. Certain ion exchange resins such as indion 204, indion 264, Amberlite IRP 64, Indion 414 etc are being used for stabilizing these drugs. Ion-exchange resin can form complex with nifedipine and its utility used to withstand drug in light environment. After going through literature it was come to know that now a day's ion exchange resins are being used for various purposes in pharmaceutical industry as above explained, and there is no sustained release photostable formulation of nifedipine using ion exchange resin. The photodegradation takes place when absorption spectrum of drug matches with that of source or incident radiation. The direct reaction occurs when these substances absorb light energy directly which will lead to intermediate products and these intermediates are converted to stable molecules by indirect reaction. The basic thing behind these reactions is to convert these substances into stable molecules. While going through literature it was found that the ion exchange resin were used as sustained release ingredients, taste masking ingredients, and certain resins indion 104 and 264 have been used for photostability. So the aim of present research attempt was made to stabilize the nifedipine, a photosensitive drug, by using indion 234 through drug-ion exchange resin complex (resinate) to design suitable drug delivery system of stable drug complexes.

METHODS AND MATERIAL

Materials

Nifedipine was provided as gift sample from J. B. Chemicals and Pharmaceuticals Ltd. Mumbai, India. Indion 234 was gifted by Ion Exchange (India) Ltd., Mumbai, India. Methanol, HPMC K-100 and HPMC E15 was supplied from S.D. Fine Chemicals Limited, Mumbai. All the chemicals and reagents were used of AR Grade.

Linearity curve

The stock solutions were prepared by dissolving 10 mg of nifedipine in 100 ml of solvents at each time (methanol and 0.1 N HCl) and spectrum was run in the wavelength range from 200 nm to 400 nm. The various dilutions were made and absorbances were measured at 233 nm in photographic mode to record calibration curve in three of solvents respectively.[11]

Preparation of drug-resin complexes (resinates)

Resinates were prepared by the batch process. An accurately weighed amount of a nifedipine (100 mg in all instances) was taken in 100 ml of methanol. Then a known weight of ion exchange resin was added in ratio of drug-resin, 1:1, 1:2 and 1:4 to the solution and stirred on a magnetic stirrer until equilibrium was achieved. Time to reach equilibrium was determined by periodically measuring concentration of the drug in solution spectrophotometrically. The solution was equilibrium at 3 hours, continues stirred on magnetic stirrer at each time. Resinates obtained were separated by filtration, washed with copious quantity of methanol to

remove uncomplexed drug. The complexes were dried overnight in a hot air oven at 40°C and then stored in tightly closed dessicator. The amount of drug loading was determined by finding the difference between the amount of drug present in the stock solution and the amount remaining in filtrate at the end of equilibrium.[6]

Drug loading analysis of complex

Firstly the weighed quantity of resinate (90 mg) equivalent to normal dose of drug (20 mg) extracted into chloroform by shaking. The solution was kept on magnetic stirrer for 3 hours. The solution is then filtered and filtrate is evaporated to dryness. The residue remained is diluted with methanol equivalent to 10 µg/ml concentration of drug. The absorbance was recorded at 233 nm and concentration was determined from calibration curve.[12]

Effect of pH on drug loading

The effect of pH on drug loading was studied by evaluating the loading at different pH conditions. Indion 234 was subjected to different pH condition to find the optimum pH condition for loading of drug. The ratios of drug and resin complexes were1:1, 1:2 and 1:4 with resin. Firstly the measured amount of drug was added to 100 ml of methanol. Then the pH of solutions was adjusted to 1. The resin (200 mg) was added and the solution was stirred for 3 hours. Drug loading was calculated by finding difference between concentration of drug in solution before and after the process. The same procedure is followed at different pH of solution (2, 3, 4, 5, 6, and 7) at each time.

FT-IR Spectroscopy

The resinate was characterized by FT-IR spectra by preparing KBr pellets at scanning range of 4000-400 cm^{-1} using a Shimadzu FT-IR spectrometer.[13]

DSC study

The physical state of resinate in the samples was determined by Differential Scanning Calorimetry (DSC) using SDTQ 600 V 20.9 BUILD 20, Universal V4.5ATA instrument. Samples containing 3mg resinate of drug were placed in the aluminum pans and heated from 10^0C to 350^0C at a heating rate of 10^0C/min under inert atmosphere flushed with nitrogen at the rate of 20 ml/min.[4]

Photostability study of complexes by irradiadiation test

The photostability study of complexes was carried out at ambient temperature and pressure. The light sources used was according to option 2 (1) given in the ICH guidelines.[6,8] For the purpose of photostability study of resinates prepared, artificial light sources were used. A tungsten lamp of 40W powers and a fluorescent lamp of 15W were used in a dark cabinet (1 m × 1 m × 0.75 m). All experiments were conducted at ambient temperature and pressure conditions. The samples were placed in 10 ml vials, 50 cm apart from light source. The weighed quantity (10 mg) nifedipine powder samples were placed for study and analyzed at 0, 3, 6, 9, 12 days. The methanolic solutions of nifedipine of concentration 10 µg/ml were placed for irradiation for 0-240 minutes (4 hours). The samples were analyzed at 0, 15, 30, 45, 60, 120 and 240 minutes. The prepared resinates was also irradiated for the period of 4 weeks. The samples were analyzed at 0, 1, 2, 3, 4 weeks.[6]

Drug dissolution test of drug through resinates

The *in-vitro* dissolution studies were performed for nifedipine and all resinates using USP XXII dissolution test apparatus type II (Electro lab) maintained at 50 rpm. Nifedipine pure drug 20 mg and resinates equivalent to 20 mg of nifedipine were accurately weighed and used in each test. The dissolution studies were carried out using 900 ml of 0.1 N HCL (containing 10% methanol), maintained at 37 ± 5°C was used as dissolution media to maintain the sink condition. The release of nifedipine was measured by withdrawing 10 ml aliquot samples at regular time intervals and withdrawn volume was replaced with fresh quantity of dissolution medium.[14] The withdrawn samples were filtered through whattman filter paper and suitably diluted with buffer assayed by using Shimadzu UV-spectrophotometer at 233 nm. The % cumulative drug release after every time intervals was calculated and reported.

RESULT AND DISCUSSION

The most obvious result of drug photodecomposition is loss of potency of the product; therapeutically inactive a more pronounced is the degraded product is toxic. Stability testing is therefore an essential part of product development and there is need to ensure that satisfactory product quality is maintained during practical usage. Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution. The step by step studies were carried out to ion-exchange resin to provide stability to the drug. For preparation of resinates, batch method was preferred because of its convenience. For the calibration of nifedipine in various solvents the UV spectrum of nifedipine was recorded and the maximum absorption of nifedipine was found to be at 233 nm (figure 2). It was found to be satisfactory with the results of work carried out by Alagar Raja M. [15] On the basis of Identification by UV spectroscopy, organoleptic properties and other tests, it was concluded that the received sample of nifedipine was pure and it should be used in the formulation of the drug delivery system.

Linearity curve of nifedipine in methanol and 0.1 N HCL

Linearity curve of nifedipine in methanol and 0.1 N HCl were recorded at 233 nm for the purpose of evaluating the drug loading analysis and photostability study. The linearity of nifedipine in methanol and 0.1 N HCl were found to be in the range of concentration from 5-50 µg/ml (figure 3) and 5-25 µg/ml (figure 4) respectively.

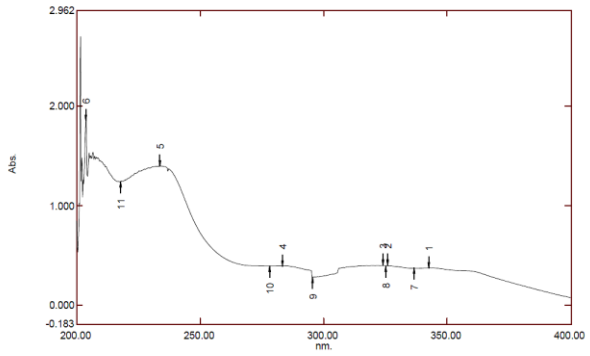

Fig. 2: UV spectrum of nifedipine.

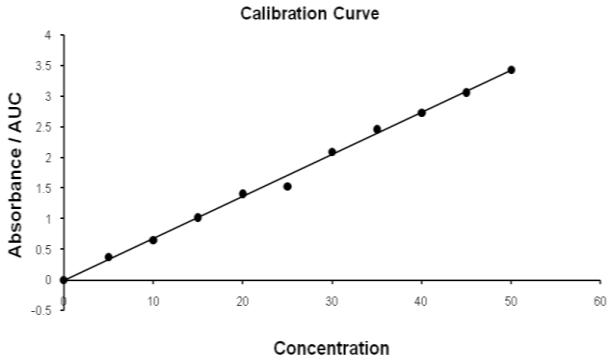

Fig. 3: Linearity curve of nifedipine in methanol.

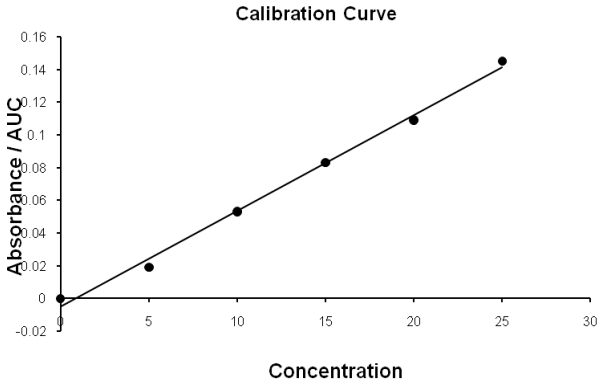

Fig. 4: Linearity curve of nifedipine in 0.1 N HCL.

Preliminary trial for formation of resinate at different drug to resin ratio

Resinates were prepared by batch process due to certain advantages like ease of operation and maximum efficiency. Also the swelling efficiency in batch process gives more surface area for drug to be entrapped in the resin. Various experimental conditions were optimized to get optimum drug loading. Various trial batches for formation of complex and drug loading analysis were carried out to study the effect of drug resin ratio on drug loading. Effect of drug: resin ratio on loading is shown in figure 5. It shows that 1:2 drug: resin ratio shows maximum drug loading. Increase in amount of complexing agent increases the loading but the amount of drug per gram of resinates decreases as ratio increased. The result shows that maximum loading was obtained at 1:2 drug resin ratio.

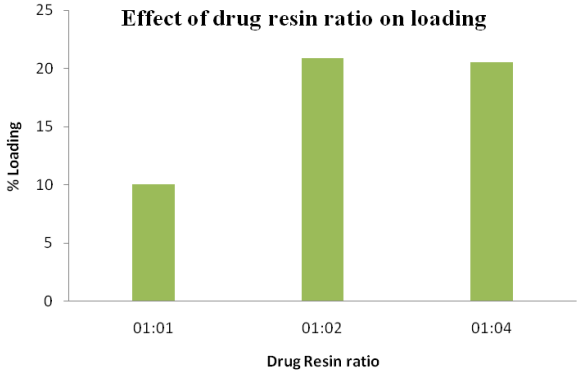

Fig. 5: Effect of drug: resin ratio on drug loading.

Effect of pH on drug loading

As the process of ion exchange is diffusion process it will take certain time for equilibrium. The time for optimum loading was found to be 6 hours. The process is also dependent upon the presence certain charged particles in the solution for exchange. Hence process is pH dependent. To study the effect of pH on drug loading the drug resin ratio was kept constant (1:2) and the loading was calculated at various pH conditions. The results are shown in figure 6 which states that the loading was found to be increased with increased with increase in pH upto pH and highest loading was found to be at pH 6. This depends upon the presence of ionic species in solution; hence drug was in ionic form at pH 6. After this it will be in unionized form so the loading goes on decreasing. Increase in the amount of complexing agent increases the amount of drug adsorbed as number of sites increases, but the drug content per gram of the complex decreases. Thus resinate prepared by batch method using indion in drug: resin ratio of 1:2 at pH 6 gave optimum drug loading.

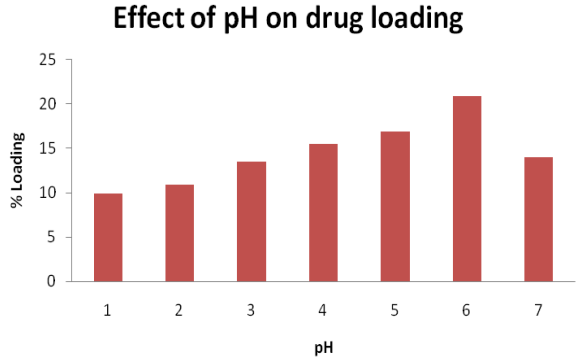

Fig. 6: Effect of pH on drug loading

Conformation of complex formation by FTIR and DSC

The complexation was confirmed by carrying out IR spectroscopy and DSC studies on indion 234 resins, drug, drug complex, and physical mixture of two. The increase in % transmittance indicates the formation of complex. Pure nifedipine showed IR absorption bands at 1678 cm^{-1} for the ester carbonyl stretching band, 1120 and 1226 cm^{-1} for ether absorption bands of C3 and C5, respectively (figure 7).

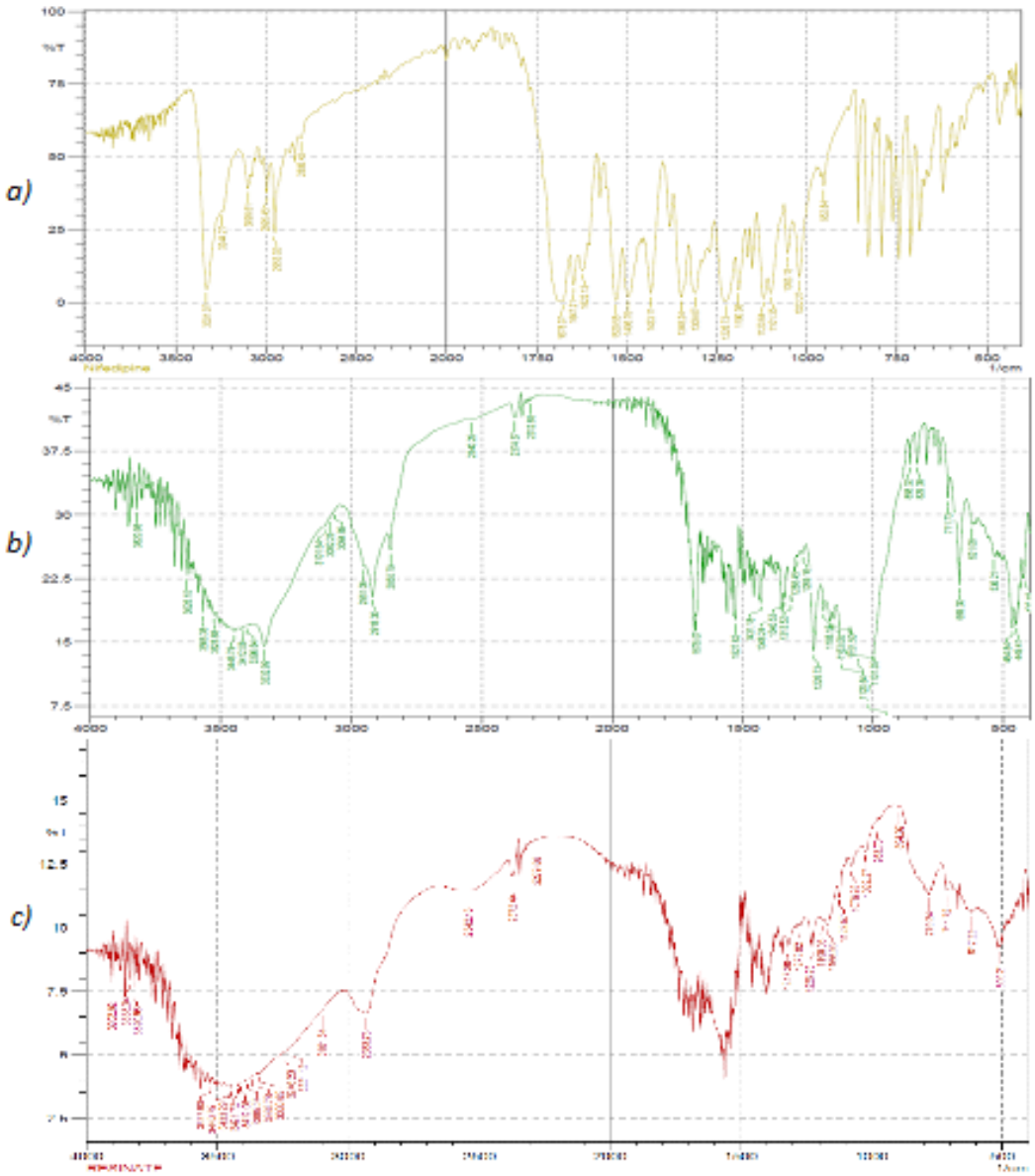

Fig. 7: FTIR spectrum of a) nifedipine, b) physical mixture of drug and resin, and c) resinate.

The absorption bands at 1496 and 1529 cm^{-1} were denoted for stretching vibration of C=C in the aromatic ring while, 1309 cm^{-1} was denoted for NO2 group and 3331 cm^{-1} for N–H group. The IR spectra of the unexposed physical mixture of nifedipine with indion 234 shows the same absorption bands for NH, C–H aromatic stretching, C–H alkyl stretching, C=O carbonyl stretching and NO_2 stretching and similarity in the finger print region indicated drug is compatible with resin. The spectra of resinate did not show new peaks indicating no chemical bond was created in resinate. The results of IR are supported by DSC analysis which states formation of complex (figure 8).

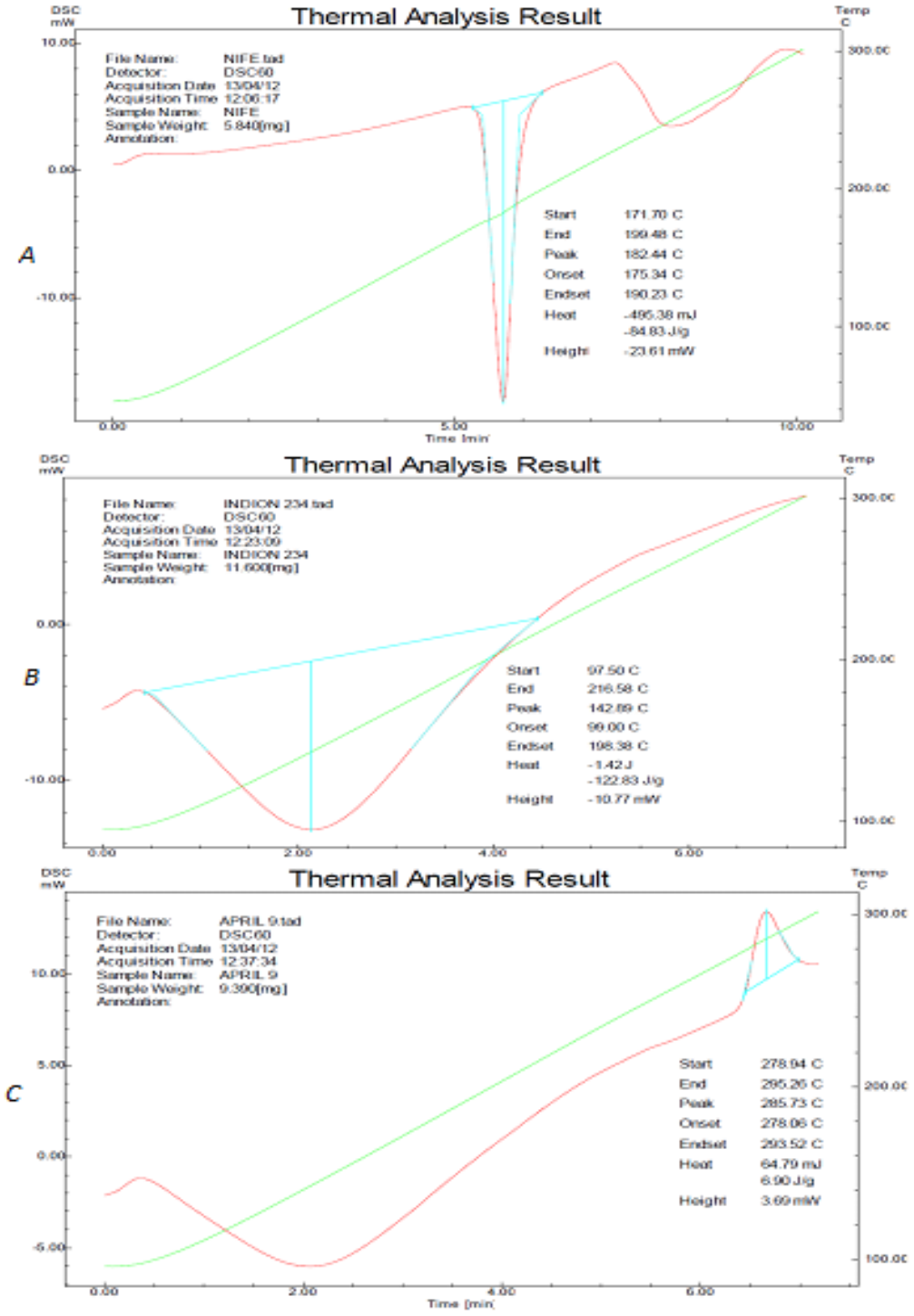

Fig. 8: DSC thermograms of A) nifedipine, B) resin, and C) resinate.

DSC illustrates the DSC thermogram of nifedipine, indion 234 and resinate of nifedipine. The DSC thermograms of nifedipine on the one hand produced melting endotherms of pure drug at 171.70^{o}C and resinate on the other, disappeared endotherms of pure drug at 171.70^{o}C. Differential scanning calorimetry thermograms indicated that nifedipine was incorporated in an amorphous state in resinates.

Photostability study of complexes

Photostability of nifedipine was determined after exposing the drug to various light sources. The light sources used include fluorescent light and tungsten lamp. The fluorescent light meets the requirement of ICH Q1 B guideline for photostability study of new drug substances and products. The methanolic solution of nifedipine was found to be degraded very rapidly as compared to powdered drug (table 1).

Table 1: Photostability of nifedipine.

Sample	Time		15 W Fluorescent lamp	60 W Tungsten lamp
Methanolic solution of Nifedipine	Minute	0	100	100
		15	90.44	85.29
		30	87.2	81.47
		45	83.82	78.67
		60	81.17	63.52
		120	75.88	43.38
		240	62.79	40.14
Nifedipine drug	Days	0	100	100
		3	84.26	70.44
		6	79.26	64.85
		9	74.11	58.08
		12	69.41	54.26
Methanolic solution of nifedipine resinate	Weeks	0	100	100
		1	99.11	98.82
		2	98.52	97.5
		3	96.91	96.61
		4	96.76	95.29

It was found to degrade completely within 4 hours of time. The powdered nifedipine when exposed to light source it was found to be degraded slowly as compared to the methanolic solution. It was found to be degraded upto 16-32 % when exposed to fluorescent light and tungsten lamp respectively. It was also found that the efficacy of tungsten lamp in photodecomposition of nifedipine is more than fluorescent lamp used for study. The resinate prepared by batch method when exposed to fluorescent light, it was found to be degraded very slowly as compared to both of above samples (methanolic solution and nifedipine powder). The resinates were analyzed weekly for successive four weeks and the results obtained show that there is no appreciable degradation of drug in resinate even after four weeks. The degradation of nifedipine from resinate was found to be less than 5% after 4 weeks. From above results certain things should be discussed, the degradation of nifedipine was found to be more in tungsten light as compared to fluorescent light. The decomposition of nifedipine was found to be more in methanolic solution form as compared to solid powder form. The degradation of nifedipine resinate was found to be negligible (figure 9).

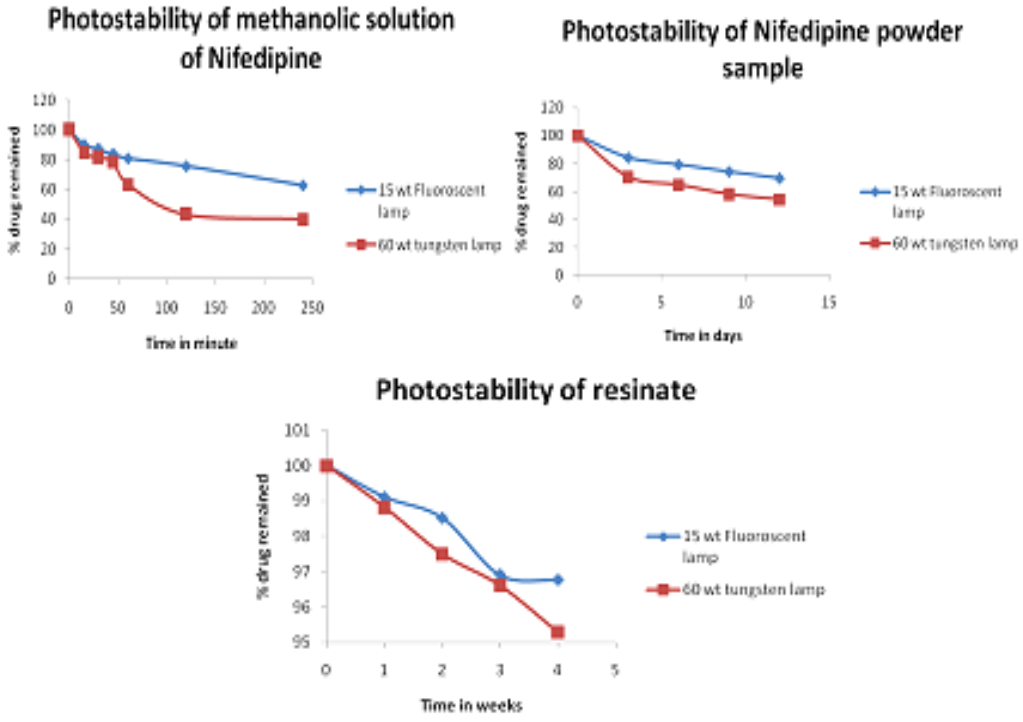

Fig. 9: Photostability of study of nifedipine in liquid and solid state.

***In-vitro* release of drug through resonates**

The release of nifedipine through resinate was illustrated in table 2. It was stated that the release of drug through ion exchange resin depends on ingoing ionic concentration and particle diffusion.[16] The release pattern shows that resin was able to sustain the release of nifedipine in very low proportion and hence for formulation of sustained drug delivery system another sustained release ingredient needs to be used. It was found to be that resin released 55% drug in just 2 hours.

Table 2: *In-vitro* release data of drug through resonates.

Sr. No.	Time (Minute)	Cumulative % drug release
1	0	0
2	15	8.970099668
3	30	18.93687708
4	45	30.56478405
5	60	43.52159468
6	75	48.50498339
7	90	51.49501661
8	105	53.82059801
9	120	55.48172757

This study indicates that nifedipine resinate prepared from drug: indion 234 (1: 2) complexes might be suitable for commercial supply dosage form.

CONCLUSION

Resinates were prepared by batch process and the formation of resinate was confirmed by using DSC and FTIR spectroscopy. The effect of drug-resin ratio and pH was also studied and the 1:2 drug resin ratio was found to be optimized. Resinates were found to be more stable than powder drug and methanolic solution. The degradation of resinates was found to be less than 5% even after 4 weeks of exposure to fluorescent light and tungsten lamp. The efficacy of fluorescent light as compared to the tungsten lamp was found to be slightly more than fluorescent light. The nifedipine was degraded rapidly in methanolic solution form, slowly in powder form and very slowly in resinate form.

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