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Investigations on Drug's Physicochemical Compatibility with Various Pharmaceutical Excipients

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ABSTRACT

Compatibility studies aimed to check the physical and chemical stability of the drug when mixed with the excipients as binary mixture. Following a comprehensive review of the literature, the oral antihypertensive agent Cilnidipine which blocks calcium channels was chosen, and talc, magnesium stearate, and polyvinylpyrrolidine were the excipients. The excipients and the drug were exposed to 40ºC/75% RH. Both a chemical and physical evaluation has been used to assess the compatibility. Physical examination is carried out on the 28th day of the study under accelerated temperature and humidity conditions by looking at the colour and texture of the binary combination. In chemical analysis, IR spectra were obtained, HPTLC and TLC were used and UV was used to estimate the drug content. After the 28th day, the drug's texture and colour remained unchanged. Using ethanol as a solvent in the UV, the regression equation derived from the linearity curve was used to determine the percentage drug concentration in each binary mixture, which was found to be greater than 98%. For HPTLC and TLC, Silica GelF254 precoated plates and a 60:40 toluene:ethyl acetate mobile phase were utilised. The Rf values of the drug in binary combinations and the drug alone revealed comparable values. The KBr pressed pellet technique was used to record the FTIR spectrums of both pure drug and binary combinations. Taking into account that no additional peaks have been detected by FTIR and no significant changes in Rf by TLC and HPTLC, physical characteristics, drug content by UV, of the drug and excipients. It can be deduced from these storage conditions that Cilnidipine was stable when tested with different excipients or in its pure form.

KERWORDS: Compatibility, Cilnidipine, Excipients, Humidity, Temperature

INTRODUCTION

A complete characterization and understanding of physicochemical interactions of an active pharmaceutical ingredient (API) in the dosage forms is an integral part of preformulation stage of new dosage form development as it is most desirable for consistent efficacy, safety and stability of a drug product. In a dosage form, an API comes in direct contact with other components (excipients) of the formulation that facilitate the administration and release of an active component as well as protect it from the environment. Although excipients are pharmacologically inert, they can interact with drugs in the dosage form to affect drug product stability in physical aspects such as organoleptic properties, dissolution slow down or chemically by causing drug degradation. Careful selection of the excipients are required for a robust and effective formulation of dosage forms that make administration easier, improve patient compliance, promote release and bioavailability of the drug and increase its shelf life. Thus, compatibility screening of an API with excipients or other active ingredients is recognized as one of the mandatory factors and is at the fore front of drug product science and technology research.

A complete understanding of the physicochemical interactions in dosage forms is expected under quality by design prototype of drug development. The analytical methods into the initial steps of preformulation studies have contributed significantly to early prediction, monitoring and characterization of the API incompatibility to avoid costly material wastage and considerably reduce the time required to arrive at an appropriate product formulation.

Formulation scientists have explored various thermal and nonthermal analytical techniques for early prediction of suitable excipients for the dosage forms to minimize or mitigate the untoward reactions (stability issues) which arise from drug– excipient incompatibility. Till date no universally accepted protocol is available for evaluating the compatibility of drug with other components. However, a flurry of reports have appeared in the last decade that highlight the use of analytical tools used in the compatibility screening of APIs in search of suitable excipients. Frequently used analytical techniques for prospective compatibility screening studies include thermal methods such as differential scanning calorimetry, thermo gravimetric analysis,

differential thermal analysis, isothermal micro calorimetry, hot stage microscopy and other analytical analysis, isothermal micro calorimetry, hot stage microscopy and other analytical methods namely powder xray diffraction, FTIR ,SEM and HPLC. Relatively newer spectroscopic techniques like solid state Nuclear Magnetic Resonance spectroscopy and near Infrared spectroscopy having potential applications in the analysis of pharmaceutical solids, have been extended to study the drug–excipient or drug moisture interactions that may lead to instability of the active principles. These techniques vary in their working principles, mechanical and thermal stress that is applied to the sample, time of analysis and amount of sample required, sensitivity of the technique to minute changes, and the necessity of internal or external standards. Moreover, some of the reported methods for the assessment of compatibility have poor predictive value while a few of them possess time consuming exercise in the pharmaceutical product development.

The safety, efficacy, quality and stability of a formulation are the substratum of any new drug development process. In order to consistently maintain these attributes in a finished dosage form, it is important to have a comprehensive understanding of the physicochemical characteristics of the Active Pharmaceutical Ingredient (API), as well as all other components (e.g. excipients, manufacturing aids, and packaging materials) of the drug product.

Due to the intimate contact of the API with one or more excipients in a formulation, there exists a likelihood of physical or chemical interactions between them. Any such interactions may result in a negative impact on the physical stability or performance attributes of the drug product. The choice of excipients is of crucial importance to avoid these negative effects, and to facilitate the development of a robust and an effective formulation.

Recent advances in various thermal and non-thermal analytical techniques have led to an improved efficiency in the detection, monitoring and prevention of the incompatibilities.

The aim of the present study is to evaluate the compatibility of the Cilnidipine with a few excipients using some physicochemical methods like visual examination, UV, TLC and FTIR techniques

Compatibility testing's objectives were

- Finding excipients that work well with a formulation
- Determining stable conditions for storage

Cilnidipine is categorised as an oral hypertensive agent that blocks calcium channels. A thorough review of the literature showed that methods for estimating the dosage and pure forms of Cilnidipine had been documented. These techniques include electrochemistry, HPLC, spectrofluorimetry, and UV-VIS spectrophotometry.

MATERIALS AND METHODS

Apparatus

Standard flasks, Measuring cylinders, Pipettes, Glass rods, Watch glass, Mortar and pestle

Spatula Beakers Capillary tube and Glass vials with rubber top were the apparatus used in this study.

Chemicals

Cilnidipine (pure drug) was generously provided by Dr. Milton’s Labs Pvt.Ltd , Chennai.

Magnesium stearate, Talc was purchased from Spectrum reagents and chemicals Pvt. ltd , Edayar , cochin. Polyvinylpyrrolidone (PVP) and Sodium chloride was obtained from SD fine- chemicals Ltd., Mumbai, India. Ethylacetate and Toluene were procured from Spectrum reagents and chemicals Pvt. Ltd, Edayar , Cochin. Ethanol was used as the solvent and was supplied by Changshu Hangsheng fine chemicals. Co. Ltd. Silica gel 60 F 254 was purchased from Merck life science Pvt. Ltd., Mumbai.

Instruments

Digital balance (Ishtaa, Technico), Spectrophotometer (Shimadzu UV-1800) Ultrasonicator (Lab man scientific instruments), FTIR (IRspirit, Toshvin analytical pvt lmt), HPTLC (linomat 5, Camag) UV light (camag-UV), Hot air oven (labtherm) Centrifuge (R-8C, Technico). The above mentioned instruments were used in the current study.

Methods

- Accurately weighed 100mg of Cilnidipine and 100mg of excipients like magnesium stearate , talc , polyvinylpyrrolidone(PVP) separately.
- Triturate each of the excipients with Cilnidipine by using mortar and pestle to form a binary mixture.
- These mixtures were then transferred in to Glass vials and closed with rubber cap and sealed it with aluminium foil.
- The above procedure is followed for Cilnidipine and Excipients alone.
- These mixtures were then kept in a hot air oven at a desired temperature of 40◦C
- ±75%RH for 28 days.
- Then it was subjected to physical and chemical examinations.

Physical Examination

The organoleptic parameters (colour and texture) of samples were checked after the storage period to check any physical incompatibility is there between drug/drug-excipient combinations.

UV-Spectroscopic Studies

Absorption spectra were collected with UV-Vis spectrometer (SHIMADZU UV-1800) equipped with computer software UV probe using a 10 mm path length quartz cell over the wavelength range from 200 to 400 nm.

Selection of Appropriate Wavelength Range

The absorbance spectrum of free Cilnidipine standard solution with a concentration of 3.5 mcg/mL was scanned from 200 to 400 nm against ethanol as blank. The wavelength range with maximum sensitivity of measured absorbance (absorption maxima) was selected.

Preparation of Standard Stock Solution

Weighed accurately 50mg of Cilnidipine and transferred in to 50ml standard volumetric flask. It was dissolved properly in ethanol and made upto the mark to get the concentrations of 1000µg/ml. Pipette out 0.1ml from the above stock solution and transferred into 10ml standard volumetric flask and made upto the mark with ethanol to get the concentration of 10µg/ml.Pipette out 1ml, 2ml, 3ml, 4ml, 5ml, from the above solution and transferred into 10ml standard volumetric flask and made up to the mark with ethanol.

Selection of Linear Concentration Range

Free Cilnidipine standard solutions with a concentration range of 1-5mcg/mL were scanned within the selected wavelength rage and the multi-point calibration curve was plotted. The concentration range that showed linear response to drug concentration was selected for calibration.

Analysis of Test Drug– Excipient Mixtures

Each sample solution of drug excipient mixture was prepared in duplicate and absorbance of the drug – excipient mixtures were measured in the selected wavelength range in the similar way as that of pure drug alone at room temperature (25 °C). Each sample was run for three scans and percentage drug content was estimated using the equation obtained from the linearity curve.

HPTLC and TLC Methods of Analysis

A CAMAG chromatographic system (Camag, Switzerland) having Linomat 5 applicator has been used. Developing twin trough chamber for plates 10 x 10 cm, with glass lid, CAMAG dual wavelength UV lamp and a viewing box (two wavelengths, 254 and 366 nm). Precoated silica gel 60 F254 aluminium TLC Plates and Precoated silica gel 60 F254 aluminium HPTLC Plates(Merck,

Germany) has been used as the stationary phase. Stock solutions were prepared in ethanol (1 mg/mL concentration). The control solutions were obtained from stock solutions by dilution in an optimal ratio depending on the intensity of the preliminarily obtained spots. Samples (2.0 µL) were applied using Linomat 5 device. The distances between the spots were set at 7 mm, and the length of the edge of the TLC plate was set at 8 mm. After the TLC and HPTLC plates were dried using a hair drier the plates were developed in a chamber previously saturated with mobile phase (Toluene : Ethylacetate, AR Grade) vapours for 30 min. The ascending mode at room temperature was used (22±2°C) until the solvent front reached 7 cm distance. Further, the plates were dried 15 min in air, and the spots were revealed using the dual wavelength UV lamp at 254 nm. Bands and spots of drug alone and Drug excipients Mixtures were made separately in HPTLC AND TLC plates respectively and developed using the above mentioned chromatographic conditions.

Preparation of samples for FTIR

Potassium Bromide pellet method was used in the study. Test samples were prepared by physical mixing of Cilnidipine and excipients in different ratios. Initially, potassium bromide was powdered and dried in oven for 45min. 100mg of potassium bromide power was mixed with 2mg of each sample, thoroughly triturated in mortar and pestle. A portion of mixture was compressed using IR pelletizing press. Then the KBr pellet was placed in sample holder of FTIR. The spectra were recorded in the wave number region of 4000-500cm-1. In each case the spectra was compared with the pure Cilnidipine spectrum to detect the interactions between drug and excipients.

RESULTS

Physical Examination

The organoleptic parameters (colour and texture) of samples were checked after the storage period to check any physical incompatibility is there between drug/drug- excipient combinations.

Table 1: Physical Examination

Sl no.	Contents	Ratio	Colour and Texture
1.	Drug alone	-	Light yellow, crystalline powder
2.	Drug + Polyvinylpyrrolidone (PVP)	1:1	Light yellowish white, fine powder
3.	Drug + Magnesium stearate	1:1	Light yellowish white, fine powder
4.	Drug + Talc	1:1	Light greenish to white, fine powder

UV-Spectroscopic Studies

Absorption spectra were collected with UV-Vis spectrometer (SHIMADZU UV-1800) equipped with computer software UV probe using a 10 mm path length quartz cell over the wavelength range from 200 to 400 nm. The drug showed its maximum absorbance at 243nm.

Selection of Appropriate Wavelength Range

The absorbance spectrum of free Cilnidipine standard solution with a concentration of 3.5 mcg/mL was scanned from 200 to 400 nm against ethanol as blank. The wavelength range with maximum sensitivity of measured absorbance (absorption maxima) was selected, and it was found to be at 243nm.

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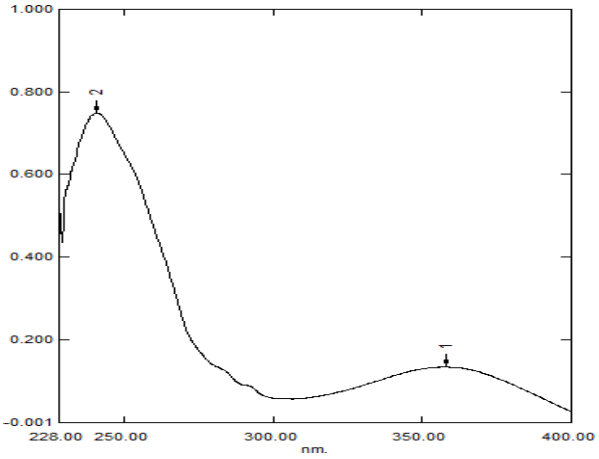

Figure 1: Absorption Spectrum of Cilnidipine

Selection of Linear Concentration Range

Free Cilnidipine standard solutions with a concentration range of 1-5mcg/mL were scanned within the selected wavelength rage and the multi-point calibration curve was plotted. The concentration range that showed linear response to drug concentration was selected for calibration. (Fig 2, Table 2)

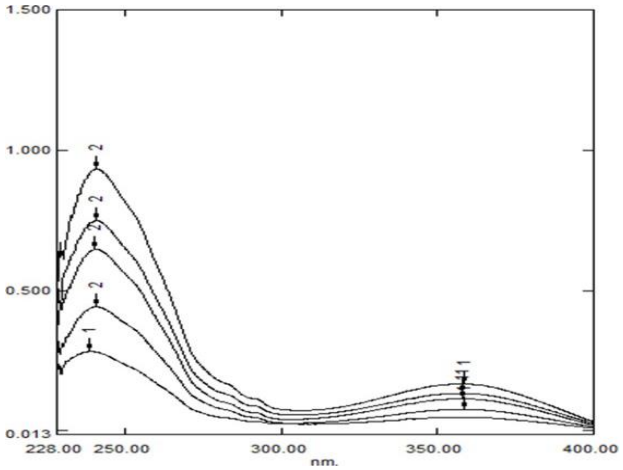

Figure 2: Overlay Spectrum of Cilnidipine

Table 2 : Calibration curve data

Sl.no	Concentration (Mcg/ml)	Absorbance
1	1	0.227
2	2	0.442
3	3	0.643
4	4	0.798
5	5	0.932

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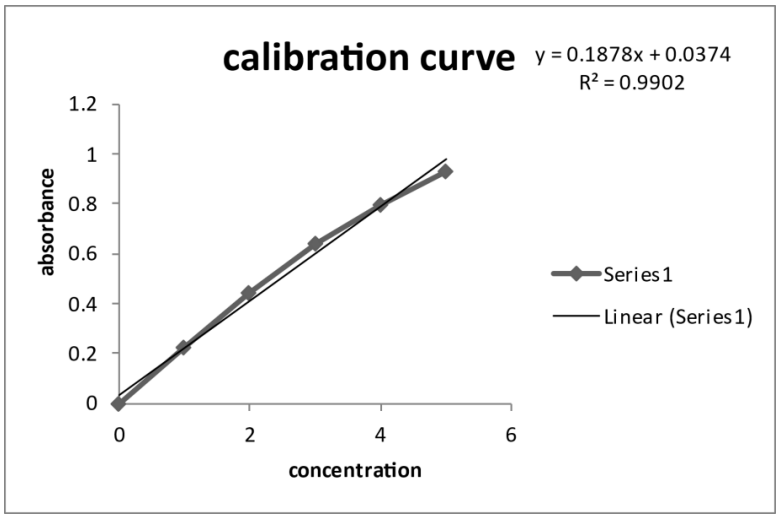

Figure 3: Linearity Curve

Analysis of Test Drug– Excipient Mixtures

Each sample solution of drug excipient mixture was prepared in duplicate and absorbance of the drug – excipient mixtures were measured in the selected wavelength range in the similar way as that of pure drug alone at room temperature (25 °C). Each sample was run for three scans and percentage drug content was estimated using the equation obtained from the linearity curve.

Table 3 : Drug content determination by UV method.

Sl no.	Contents	Ratio	%Drug content	SD	% RSD
1.	Drug alone	-	99.98%	0.99	1.103
2.	Drug+Polyvinylpyrrolidone (PVP)	1:1	98.01%	0.08	1.109
3.	Drug+ Magnesium stearate	1:1	100.03%	0.11	1.89
4.	Drug + Talc	1:1	100.11%	0.36	1.49

HPTLC and TLC Methods of Analysis

A CAMAG chromatographic system (Camag, Switzerland) having Linomat 5 applicator has been used. Developing twin trough chamber for plates 10 x 10 cm, with glass lid, CAMAG dual wavelength UV lamp and a viewing box (two wavelengths, 254 and 366 nm). Precoated silica gel 60 F254 aluminium TLC Plates and Precoated silica gel 60 F254 aluminium HPTLC Plates (Merck, Germany) has been used as the stationary phase. Stock solutions were prepared in ethanol (1 mg/mL concentration). The control solutions were obtained from stock solutions by dilution in an optimal ratio depending on the intensity of the preliminarily obtained spots. Samples (2.0 µL) were applied using Linomat 5 device. The distances between the spots were set at 7 mm, and the length of the edge of the TLC plate was set at 8 mm. After the TLC and HPTLC plates were dried using a hair drier the plates were developed in a chamber previously saturated with mobile phase (Toluene : Ethylacetate, AR Grade) vapours for 30 min. The ascending mode at room temperature was used (22±2°C) until the solvent front reached 7 cm distance. Further, the plates were dried 15 min in air, and the spots were revealed using the dual wavelength UV lamp at 254 nm. Bands and spots of drug alone and Drug excipients Mixtures were made separately in HPTLC and TLC plates respectively and developed using the above mentioned chromatographic conditions.

Table 4 : Chromatographic conditions

Sl no.	Particulars	TLC	HPTLC
1.	Plates	TLC Silica gel F254	HPTLC Silica gel F254
2.	Plate dimensions	10×10 cm	10×10 cm
3.	Mobile phase	Toluene: Ethylacetate (60 : 40)	Toluene: Ethylacetate (60 : 40)
4.	Detection wavelength	254nm	254nm

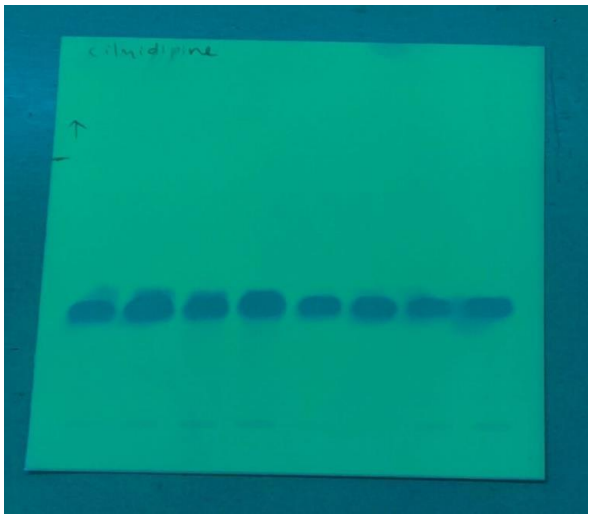

Figure 4: HPTLC Plates

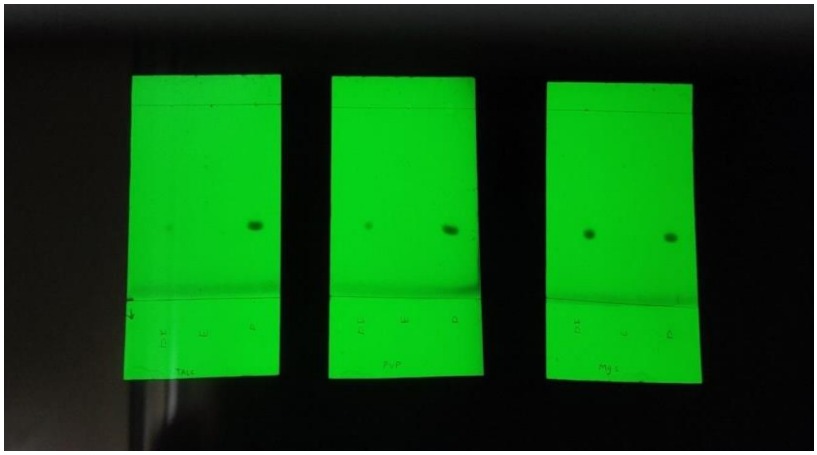

Figure 5: TLC Plates

Table 5: Rf values of Cilnidipine in TLC and HPTLC

Sl no.	Contents	Ratio	Rf value by TLC	Rf value by HPTLC
1.	Drug alone	-	5.8	5.8
2.	Drug+Polyvinylpyrrolidone (PVP)	1:1	5.6	5.7
3.	Drug+ Magnesium stearate	1:1	5.8	5.7
4.	Drug + Talc	1:1	5.7	5.8

Preparation of samples for FTIR

Potassium Bromide pellet method was used in the study. Test samples were prepared by physical mixing of Cilnidipine and excipients in different ratios. Initially, potassium bromide was powdered and dried in oven for 45min. 100mg of potassium bromide power was mixed with 2mg of each sample, thoroughly triturated in mortar and pestle. A portion of mixture was compressed using IR pelletizing press. Then the KBr pellet was placed in sample holder of FTIR. The spectra were recorded in the wave number region of 4000-500cm-1. In each case the spectra was compared with the pure Cilnidipine spectrum to detect the interactions between drug and excipients.

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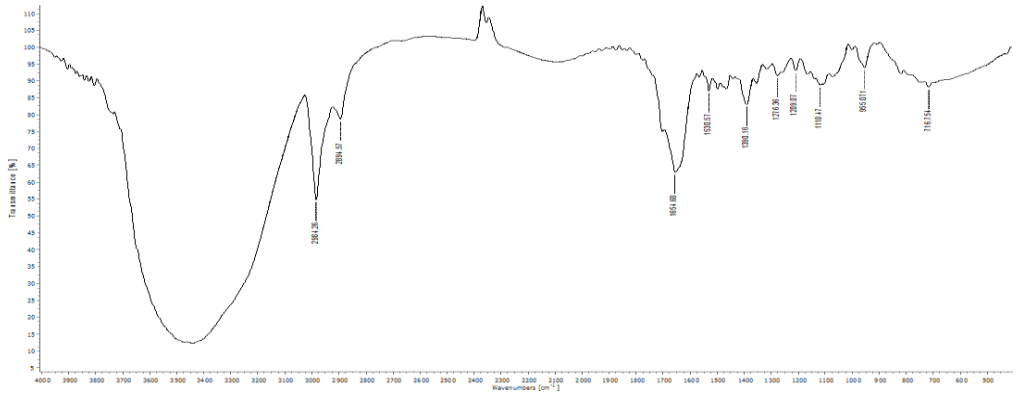

Figure 6: FTIR Spectra of Cilnidipine alone.

Table 6 : IR Interpretation.

Slno.	Functional groups	Wave no. region (cm^{-1})
1.	Aromatic 2° amine (N-H Stretching)	3320-3270
2.	Alkenes (C=C Stretching acyclic)	1680-1625
3.	Nitroso (N=O)	1290-1190
4.	Nitro (-N-O)	1357-1318
5.	Methoxy (-OCH3)	2830-2810

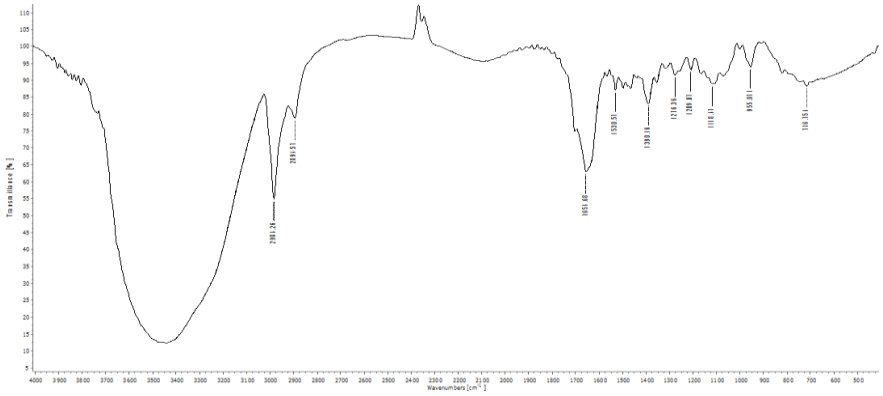

Figure 7: FTIR Spectra of Cilnidipine with PVP

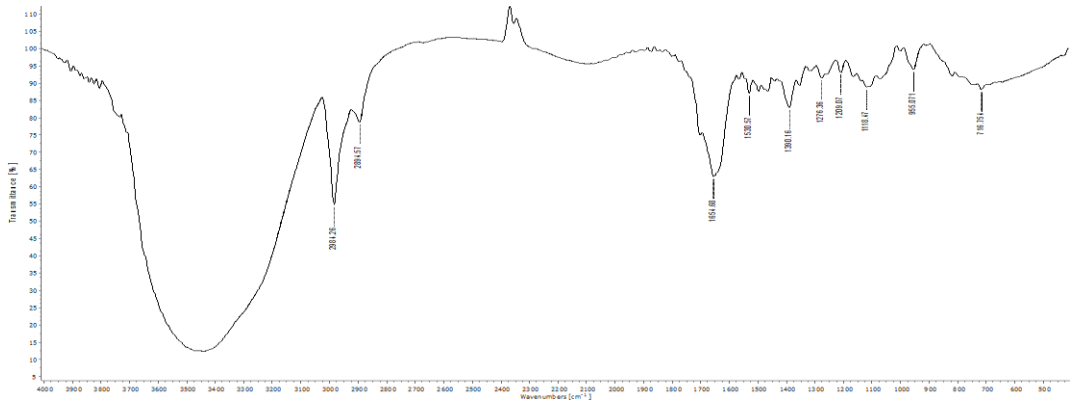

Figure 8 : FTIR Spectra of Cilnidipine with Talc

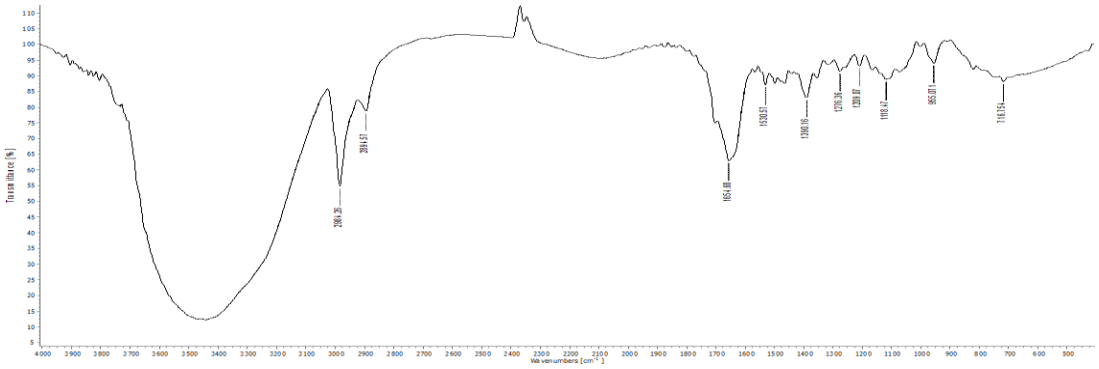

Figure 9: FTIR Spectra of Cilnidipine with Magnesium stearate

DISCUSSION

When a formulation was prepared there is a chance of incompatibility between API and Excipients used for the formulation. Despite being recognized as inert, excipients can have a substantial impact on drug stability as they can interact with drug substances. In the present investigation the incompatibility was checked by Physicochemical examinations like appearance, UV, TLC, HPTLC & FTIR. Compatibility of Cilnidipine with different excipients like Mg stearate, Talc and PVP were evaluated. The results revealed that there is no possible immediate interaction between Cilnidipine and the used excipients when stored at 40ºC for a period of 28 days with a relative humidity of 75%. Physical appearance, Percentage drug content, Rf Value and IR spectrum of pure Cilnidipine was compared to that of Cilnidipine in powder mixtures, no significant difference were observed in the Physical and Chemical parameters checked. Furthermore, neither missing in the bands nor appearance of new bands in the IR spectra or change in Retardation Factor in both TLC and HPTLC and Percentage drug content estimated by UV were Satisfactory for powder mixtures when noted at day 28 stored at 40°C and 75%RH. Pure drug Cilnidipine or Cilnidipine in binary mixtures was stable for 28 days at 40°C and 75% RH. Since there is no change in physical appearance, drug content, or change in Rf or no extra peaks reported due to the degradation products of drug and excipients. It can be deduced that the drug was stable in pure form or in the presence of excipients tested under these storage conditions. Therefore, these excipients were found to be compatible with Cilnidipine.

SUMMARY AND CONCLUSIONS

The pharmaceutical analysis has importance in the identity, strength, quality and purity of drugs and chemicals. Quality assurance plays a central role in determining the safety and efficacy of medicines. Highly specific and sensitive instruments are available for this, out of these the chromatographic and spectroscopic methods have great importance.

Compatibility studies were also aimed to check the physical and chemical stability of the drug when mixed with the excipients as binary mixture. The aim of the present study is to evaluate the compatibility of the Cilnidipine with a few excipients using some physicochemical methods like visual examination, UV, TLC and FTIR techniques after subjecting the drug to a condition of 40ºC/75% RH.

Cilnidipine is categorised as an oral antihypertensive agent that blocks calcium channels. A thorough review of the literature showed that methods for estimating the dosage and pure forms of Cilnidipine had been documented. These techniques include electrochemistry, HPLC, Spectrofluorimetry, and UV-VIS Spectrophotometry.

The present study plans to assess the chemical and physical stability of Cilnidipine in a binary mixture with excipients such as talc, polyvinyl pyrrolidine, and magnesium stearate.

The samples were kept for 28 days at an accelerated stability temperature of 40ºC and 75% relative humidity. The compatibility has been examined by physical evaluation and chemical evaluation as well. Physical evaluation is done by examining the colour and texture of the binary mixture on the 28th day of the study under the accelerated conditions of temperature and Humidity. Chemical analysis made use of UV for estimating the drug content, HPTLC and TLC given the Rf Values and IR spectra was also taken.

There was no change in texture and colour of the drug after 28th day. UV studies has been done using ethanol as the solvent at a wavelength of 243nm. The percentage drug content in every binary mixture was above 98%, it was calculated from the regression equation obtained from the linearity curve. Silical gel F254 precoated plates were used for HPTLC and TLC the Rf value of pure drug alone and drug in binary mixtures showed similar values. The study was carried out in Twin trough chamber using 10×10 cm

Plates using a mobile phase of Toluene: Ethyl acetate in the ratio of 60 :40. The FTIR spectrum of pure drug and binary mixtures were recorded by making use of Kbr pressed pellet technique. Pellets were prepared and scanned to get spectrums which was similar to that of pure drug which showed characteristic peaks. Considering that there have been no observed extra peaks because of the drug and excipient degradation products, changes in Rf, physical appearance, or drug content. Based on these storage circumstances, it may be inferred that the drug was stable either in its pure form or when tested with various excipients. Consequently, it was discovered that these excipients and Cilnidipine were compatible.

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Conflict of Interest Statement:
The authors have no conflicts of interest to declare.