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Solubility enhancement and evaluation of Cilnidipine using solid Dispersion techniques

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Abstract: The poor solubility of Cilnidipine leads to low bioavailability and limits its therapeutic efficacy. To develop a dosage form that is stable, effective and has a higher bioavailability. It is necessary to increase the solubility of such medications. The present study aimed to improve the solubility by solid dispersion technique of Cilnidipine by solid dispersion techniques. Solvent evaporation and melt fusion methods were used to prepare solid dispersions of the drug cilnidipine with various polymers. The solubility of these prepared solid dispersions was evaluated by FT-IR spectroscopy, Differential Scanning Colorimetry and X-ray diffraction. The greatest solubility, of 21.07 µg/mL, was found in the solid dispersion that was developed by solvent evaporation technique employing a combination of Cilnidipine and Poloxamer 188 in a 1:9 ratio. The current investigation showed that solid dispersion using Poloxamer 188 can be a potentially effective method to increase the solubility and rate of dissolution of cilnidipine.

Introduction

The most significant challenge in pharmaceutical preparations is the poor water solubility of hydrophobic medicines. To get the optimal drug concentration in systemic circulation and the best bioavailability to produce the intended pharmacological response, their solubility is a rate-limiting stage in the absorption process (Hasanain, 2016). The solubility of such medications can be increased by creating a formulation that promotes quicker drug dissolution than the crystalline form. (Shah, 2007; Mankar, 2021). Various techniques, including chemical and physical alterations, crystal engineering, particle size reduction, salt generation, complexation, the addition of solvent or surface-active agents, solid dispersion, and others, can be used to make drugs more soluble. The characteristics of the drug, the site of absorption, and the criteria for the dose form all influence the choice of a solubility-enhancing method (Sareen, 2012; Savjani, 2012).

Solid dispersion is the combination of two different solid products, such as a hydrophilic matrix and a hydrophobic drug. The drug may be dispersed as crystalline or amorphous particles that are molecular in nature. When exposed to aqueous solutions, water-insoluble drugs dissolve more quickly and are more bioavailable because the carrier dissolves and the drug is liberated as extremely small colloidal particles. Because of the significant reduction in particle size and increase in surface area, oral absorption and dissolving rates are accelerated. Furthermore, throughout the process of dissolving a medication, no energy is required to alter its crystal structure. The presence of nearby hydrophilic carriers may boost the drug's solubility and wettability (Kalia, 2011).

The most common sign of chronic hypertension is a blood pressure value of 120/80 mmHg or higher. It is the most significant component that may be connected to and serves as an early warning system for numerous bodily disorders. Calcium channel blockers are the most commonly used antihypertensive drugs. Cinidipine is a calcium antagonist of the dihydropyridine fourth generation. L-type and N-type calcium channels may be inhibited by it (Mohana, 2022). Cilnidipine belongs to BCS Class II with low solubility and high permeability

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which leads to low bioavailability. Cilnidipine's claimed bioavailability is 13%, and after oral administration, drug concentrations reach their peak at 1.8 to 2.2 hours, with a half-life of 7.5 hours. improvement of cilnidipine's solubility through solid dispersion utilising different polymers (Kuhikar, 2021; Chen, 2014; Mohana, 2022; Vydana, 2022) and other techniques (Liu, 2020; Diwan, 2021) also reported. Hence the basic aim of the present study is to enhance the solubility by solid dispersion technique using polymer Poloxamer 188 and increase the bioavailability of cilnidipine and make that drug available at the proper site of action within the optimum dose.

Materials and methods

Materials

Cilnidipine (Gift sample from Relington Pharma, Ahmedabad), Polyvinyl pyrrolidone K30, Polyethylene glycol 6000, Hydroxy propyl methyl cellulose (Research lab fine chemical, Mumbai), Poloxamer 188 (Gift sample from Aadhunik industries, Mumbai), Methanol (Merck Pvt Ltd, Mumbai).

Methods

Phase solubility study of the carriers

The solubilizing properties of the carrier are determined using the shake flask method. In varied concentrations (1% and 2%), aqueous solutions of various carriers, including polyvinyl pyrrolidone K30, hydroxypropyl methylcellulose, polyethylene glycol 6000 and Poloxamer 188 were prepared. The extra drug was added to these solutions to produce saturated solutions. After being shaken for 24 hours at 60 rpm in an orbital shaker, samples were centrifuged for 10 minutes at 3000 rpm. A UV-visible double-beam spectrophotometer (Shimadzu Corporation, Japan) was used to measure the supernatant after diluting it at 243 nm (Mohana, 2022; Sakure, 2020).

Drug excipient compatibility study

Studies on the compatibility of drug excipients are a crucial stage in the development of new formulations. Excipients for use in pharmaceutical formulation have either been approved or rejected using compatibility tests on drug excipients. Both the API alone and with each excipient were taken in a 1:1 ratio and thoroughly mixed. After being put through a sieve, the mixture was put into glass vials and maintained in a stability chamber at a temperature of 40± 2°C/75 ± 5% RH.

Preparation of solid dispersion

Physical mixtures

The drug and polymer were simply combined in the specified quantities using a pestle and mortar to form physical mixtures. The resulting blends were then placed in sealed vials and placed in a desiccator before being run through a #100 sieve to prevent abrasion.[9] In a phase solubility investigation, the polymer that shows maximum solubility was chosen, and solid dispersion in various ratios was prepared. By using Physical mixtures of cilnidipine with various polymers, such as PEG 6000 and Poloxamer 188 in ratios of 1:3, 1:6, and 1:9, were prepared.

Solvent evaporation method

The cilnidipine and polymer (Polyethylene glycol 6000/Poloxamer 188) were precisely weighed and dissolved in methanol according to the calculated quantities. The solution was then sonicated and stirred for 1 hour over a magnetic stirrer. After sonication methanol was evaporated by using a water bath at 60˚ C until all of methanol got evaporated. Finally, the solid dispersion had dried entirely. Crushed, put through 100# sieves, and kept in desiccators until use, the dried bulk was prepared. Table 1 lists the six batches (F1 to F6) that were prepared using the solvent evaporation process (Mohan, 2015; Bhole, 2009; Hassnain, 2022; Sayeed, 2011).

Table 1. Preparation of solid dispersion by solvent evaporation method

Batch code	Ratio	Composition
F1	1:3	Cilnidipine + PEG 6000
F2	1:6	
F3	1:9	
F4	1:3	Cilnidipine + Poloxamer 188
F5	1:6	
F6	1:9	

Melt fusion method

Solid dispersions of cilnidipine with polymer (PEG 6000 / Poloxamer 188) were prepared by melt fusion method. A precisely weighed quantity of polymer was melted at 60°C in a porcelain dish after which the necessary quantity of cilnidipine was added. After stirring the molten drug and polymer, they were quickly cooled in an ice bath. In a mortar and pestle, the obtained solidified mass was smashed before being sieved. The desiccator was used to store the obtained solid dispersion. A total of six batches (F7 to F12) by melt fusion method were prepared and are mentioned in Table 2 (Sayeed, 2016; Ahmed, 2012).

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Table 2. Preparation of solid dispersion by Melt fusion method

Batch code	Ratio	Composition
F7	1:3	Cilnidipine + PEG 6000
F8	1:6	
F9	1:9	
F10	1:3	Cilnidipine + Poloxamer 188
F11	1:6	
F12	1:9	

Evaluation of Solid dispersions

Saturation solubility study of solid dispersion and Physical mixture

The solubility investigation of the physical mixture and solid dispersion was conducted using water as the solvent. Studies on physical mixture solubility and solid dispersion were both carried out utilising the shaking flask method. The physical mixture, also known as the generated solid dispersion, was added to 20 ml of water in excess. The material was sonicated at 250°C ± 20°C for 10 minutes. The sample was shaken for 24 hours at 60 revolutions per minute in an orbital shaker before the flask was allowed to settle. After being collected, the supernatant was centrifuged at 3000 rpm for 10 minutes. A UV-visible double-beam spectrophotometer was used to measure the filtrate's absorbance at 243 nm to calculate its solubility (Mankar, 2021).

Determination of drug content

A solid dispersion containing 10 mg of cilnidipine was dissolved in 100 ml of methanol. The solution has been filtered and further diluted, and as a result, its absorbance is now within the acceptable range. The absorbance of the solution was measured at 243 nm using a UV-visible double-beam spectrophotometer (Kataria, 2014; Alam, 2013).

In vitro dissolution study

For Dissolution study of solid dispersions and a physical mixture containing 10 mg of cilnidipine, water (900 ml) was spun at 50 rpm using a basket type USP type 1 apparatus (LAB INDIA DS 8000) that was kept at a constant 37 ±0.5°C. For 60 minutes, the samples were taken at regular intervals. After pipetting out 5 ml of the dissolution media, the sink condition was maintained by adding the same amount of solvent back in. The withdrawn sample was filtered through 0.45µ Whatman filter paper and analysed at 243nm using water as a blank in a UV–visible double beam spectrophotometer. The batch that showed maximum drug release was considered an optimized batch and characterization of solid dispersion was done (Mohana, 2022; Kataria, 2014).

Characterization of solid dispersion

FT-IR spectroscopy

Using potassium bromide (KBr) as a blank, the IR spectra of the optimised batch were captured using a Shimadzu IRAffinity-1Spectrum at a resolution of 4 cm over a range of 400–4000/cm (Mohana, 2022; Sayeed, 2016).

Differential scanning calorimetry (DSC)

A Mettler Toledo Differential scanning calorimeter apparatus was used to conduct the differential scanning calorimetry (DSC) measurement in Mumbai, India. In sealed aluminium pans with nitrogen gas, an optimised solid dispersion weighing roughly 6-7 mg was heated across a temperature range of 100-150°C while being thermographed at a rate of 40 °C/min (Mohana, 2022).

X-ray diffraction study

The optimised solid dispersion was studied using X-ray diffraction (XRD). Diffractogram was obtained using an Empyrean, Malvern Paralytical multifunctional diffractometer with Multi-Core Optics (United Kingdom). The sample was examined in the 0-100° angle range.

Result and Discussion

Pre-formulation study

Determination of melting point

The melting point of Cilnidipine was found to be in the range of 110-112ºC which complies with the reported melting point of Cilnidipine.

Phase solubility study of the carriers

Phase solubility studies of drugs and carriers were performed by using different polymeric solutions of 1% and 2% of PVP K30, HPMC, PEG 6000 and Poloxamer 188. The concentration of cilnidipine in individual polymeric solutions was calculated by using the equation of line obtained from the calibration curve y = 0.0043x + 0.0169 in water. The results of the phase solubility study are mentioned in Table 3.

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Table 3. Phase solubility study of carriers

Polymer	% Polymeric solution	Absorbance obtained	Concentration obtained (µg/ml)	Concentration After multiplying with dilution factor *10 (µg/ml)	Concentration obtained (mg/ml)
PVP K30	1%	0.0229	1.405	14.05	0.0141
	2%	0.0233	1.493	14.93	0.0149
HPMC	1%	0.0209	0.923	9.23	0.0092
	2%	0.0219	1.156	11.56	0.0116
PEG 6000	1%	0.0238	1.598	15.98	0.016
	2%	0.0246	1.784	17.84	0.0178
Poloxamer 188	1%	0.0247	1.805	18.05	0.0181
	2%	0.0252	1.921	19.21	0.0192

Table 4. IR frequencies of Physical mixture

Functional group	Physical mixture (Cilnidipine: PEG 6000)		Physical mixture (Cilnidipine: Poloxamer 188)	
	Observed Frequency	Reported Frequency	Observed Frequency	Reported Frequency
N–H stretching (Aromatic 2^0 amine)	3291.89	3320-3270	3282.25	3320-3270
C=C Stretching acyclic (Alkenes)	1677.77	1680-1625	1648.84	1680-1625
N=O (Nitroso)	1266.04	1290-1190	1266.04	1290-1190
-N-O (Nitro)	-	-	1338.36	1357-1318
O=C-O-R (Ester)	1192.76	1210-1163	1202.4	1210-1163

Drug excipient compatibility study

There is no interaction between the drug and the polymer, according to the analysis of the FTIR spectra of cilnidipine in its pure form and their physical mixture. IR spectra for the compatibility study are shown in Figure 1.

Evaluation of solid dispersions

Saturation solubility study of solid dispersion and physical mixture

Utilising water as the solvent, research on the saturation solubility of solid dispersion and physical mixture was conducted. Both a solid dispersion and a physical mixture's solubility were determined using the shake flask method. Using the equation of line derived from the calibration curve in water, the concentration of cilnidipine in solid dispersion and physical mixture was estimated. Tables 5 and 6 list the findings of the saturation solubility study.

Drug content determination

The actual drug content of each of the 12 formulations is displayed in Figure 2. The solid dispersion formulations' drug content range of 94.19 to 99.98% shows that the existing methods are being used to produce solid dispersions with high content uniformity. The maximum drug content for the F6 batch was found to be 99.98%.

In vitro dissolution study

An in vitro dissolution study was performed for all the prepared batches as well as with physical mixtures of different polymers in different ratios. The percent cumulative drug release for all 12 batches was found in the 79.12 – 98.55 % range. As the concentration of polymer in solid dispersion increases percent cumulative drug release also increases with a decrease in time. Based on in vitro dissolution data it was found that the F6 batch had having highest percent cumulative drug release that is 98.55% respective to other batches. An in vitro dissolution study was also performed with physical mixtures of cilnidipine: Polymers in different ratios and results were found in a range of 25.75 – 32.88 %.

Characterization of optimized solid dispersion batch(F6)

FTIR spectroscopy for optimized batch

The FTIR spectroscopy for the optimized solid dispersion batch was performed and observed frequencies were compared with the standard IR of the pure drug

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Table 5. Saturation solubility study for Physical mixture

Physical mixture	Ratio	Absorbance obtained	Concentration obtained (µg/ml)	Dilution factor (*10) (µg/ml)	Concentration obtained (mg/ml)
Cilnidipine: PEG6000	1:3	0.0275	2.465	24.651	0.025
	1:6	0.0348	4.163	41.628	0.042
	1:9	0.0489	7.442	74.419	0.074
Cilnidipine: Poloxamer 188	1:3	0.0305	3.163	31.628	0.032
	1:6	0.0419	5.814	58.140	0.058
	1:9	0.0522	8.209	82.093	0.082

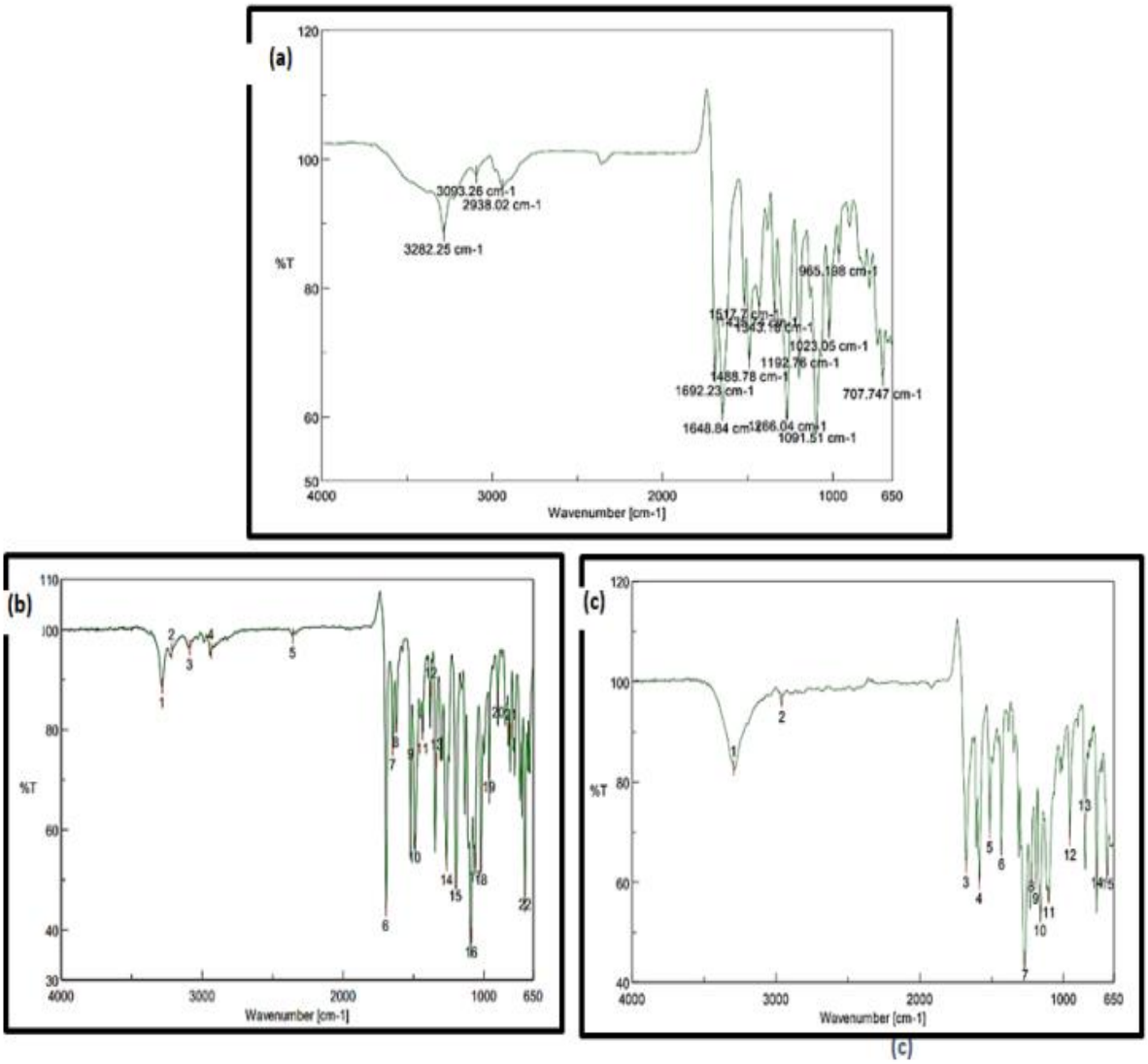

Figure 1. Drug excipient compatibility study: (a) IR of pure Cilnidipine (b) IR of Physical mixture (Cilnidipine: PEG 6000) (c) IR of Physical mixture (Cilnidipine: Poloxamer 188)

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Table 6. Saturation solubility study for Solid dispersion

Batches	Absorbance obtained	Concentration obtained (µg/ml)	Dilution factor (*10) (µg/ml)	Concentration obtained (mg/ml)
F1	0.0723	12.884	128.837	0.129
F2	0.0835	15.488	154.884	0.155
F3	0.0972	18.674	186.744	0.187
F4	0.0902	17.047	170.465	0.170
F5	0.0998	19.279	192.791	0.193
F6	0.1075	21.070	210.698	0.211
F7	0.0659	11.395	113.953	0.114
F8	0.0775	14.093	140.930	0.141
F9	0.0847	15.767	157.674	0.158
F10	0.0867	16.233	162.326	0.162

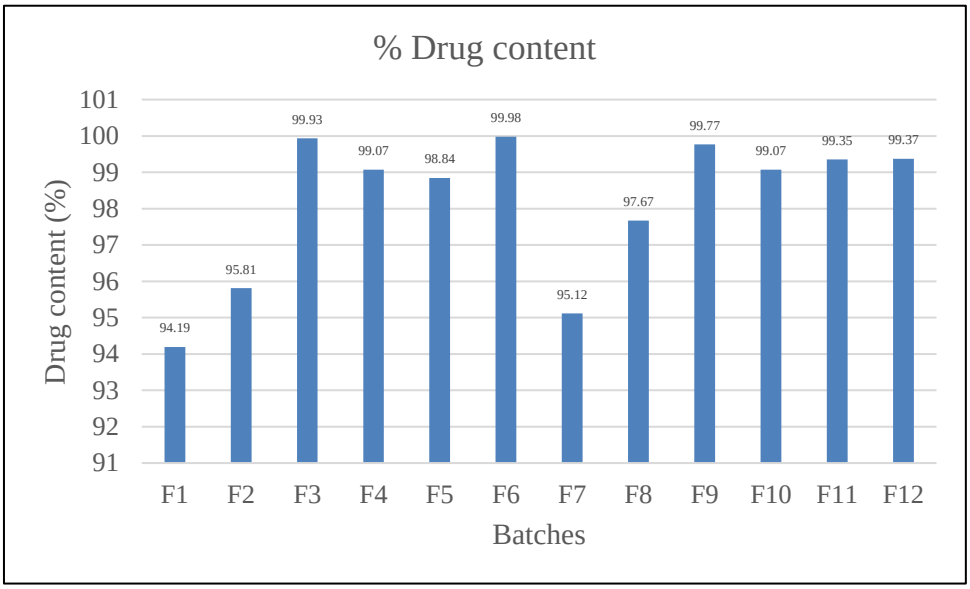


Figure 2. Percent Drug Content for all batches

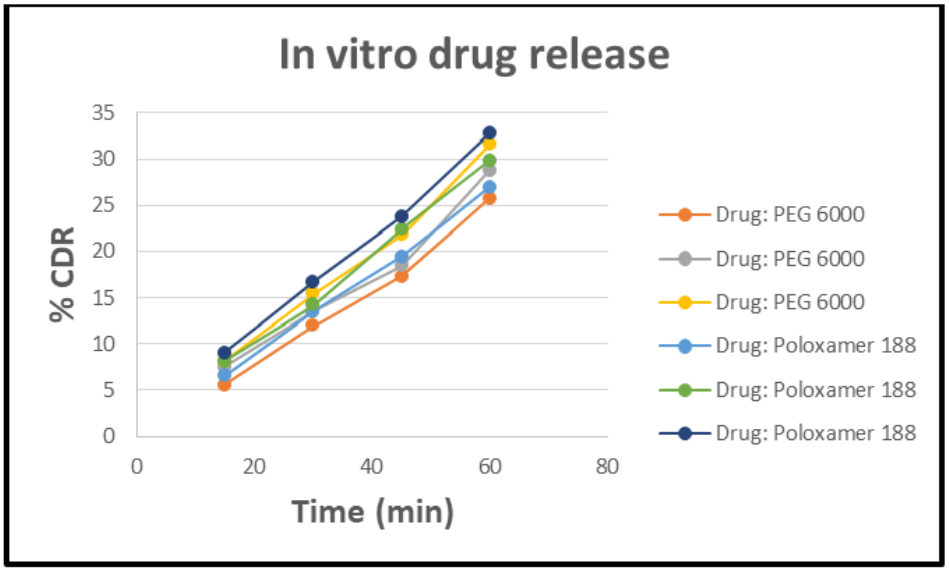


Figure 3. In vitro dissolution study for Physical mixture

Table 7. IR frequencies of pure Cilnidipine and Optimized batch of Solid dispersion functional group

Functional group	Observed Frequency		Reported Frequency	
	Cilnidipine Standard	Cilnidipine Solid dispersion		
N–H stretching (Aromatic 2^0 amine)		3282.25	3289.57	3320-3270
C=C Stretching acyclic (Alkenes)		1648.84	1697.07	1680-1625
N=O (Nitroso)		1266.04	1278.21	1290-1190
-N-O (Nitro)	1343.18	1340.32	1357-1318	1357-1318
O=C-O-R (Ester)	1192.76	1201.63	1210-1163	1210-1163

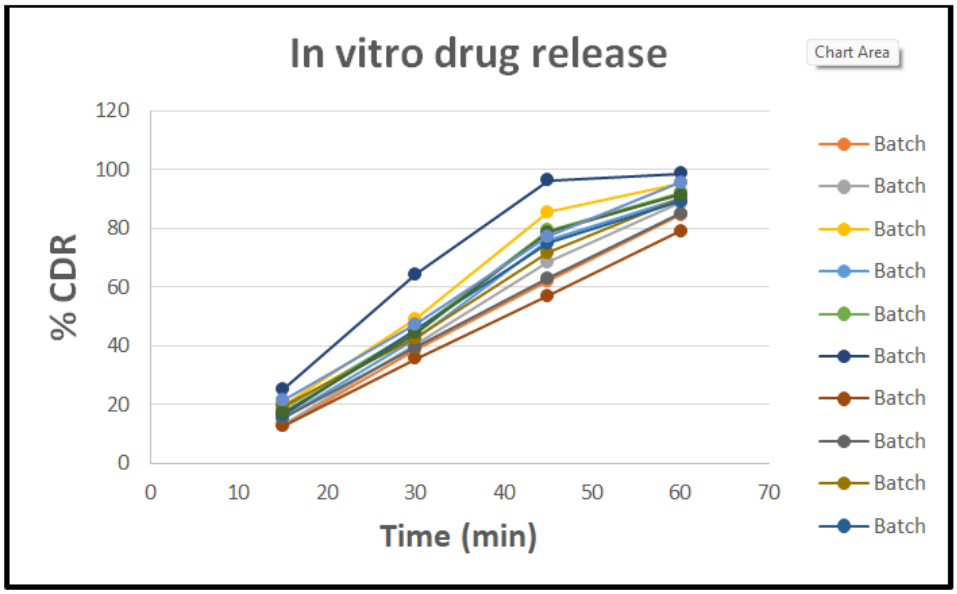


Figure 4. In vitro dissolution study for Batches

sample. The respective IR was represented in Figures 5 (a) and 5 (b). There are no differences in the positions of the absorption bands indicating the absence of significant interactions between Cilnidipine and carriers.

Differential Scanning Calorimetry (DSC) Study

Shimadzu's DSC-60 was used to take the DSC thermogram of cilnidipine and the optimised batch of solid dispersion. As a material of reference, indium was used. The sample (5 mg) was put in an aluminium pan, which was then crimped shut. At a rate of 10^0C/min, the sample and reference material were heated from ambient temperature to 375^0C.

DSC Thermogram of the pure drug (Cilnidipine) was shown in Figure 6 (a) and an optimized batch of solid dispersion was shown in 6 (b). It can be easily recognized by the presence of a sharp endothermic peak at around 86.15^0C in pure cilnidipine and 60.68^0C in the optimized solid dispersion batch.

X-ray diffraction study

The optimised batch of solid dispersion and pure drug samples (cilnidipine) were used in the X-ray diffraction research. Figures 7(a) and 7(b) contain details of the outcomes. The crystalline nature of cilnidipine is indicated by the existence of sharp peaks. The total number of peaks for the optimised solid dispersion batch and pure drug sample were 44 and 12, respectively. This indicates that the majority of the crystalline endothermic peak disappeared as well as the typical intensities of cilnidipine. This shows that solid dispersion completely converted crystalline cilnidipine into an amorphous form. The amorphous form of cilnidipine was confirmed by XRD analyses of solid dispersion systems. Based on results obtained from the evaluation of all the

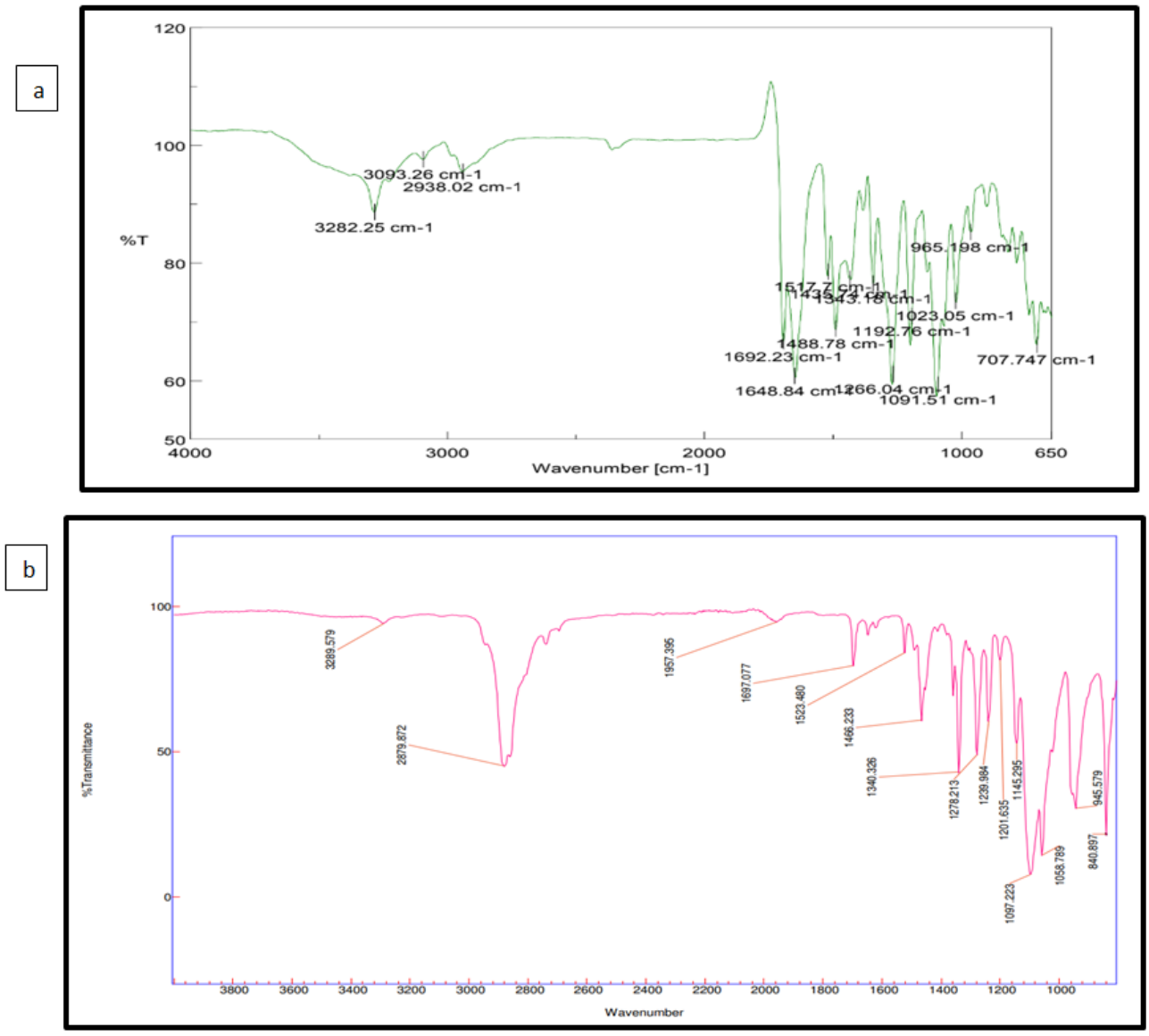
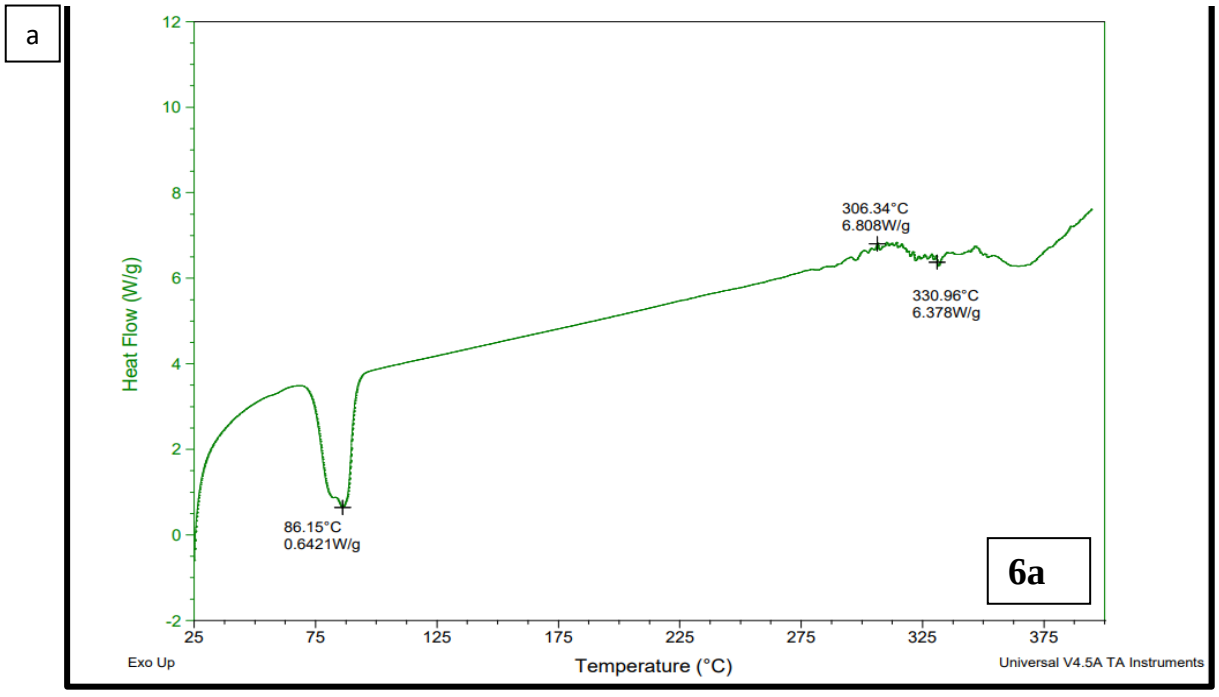


Figure 5a. IR of pure Cilnidipine b) IR of Optimized batch (Solid dispersion of Cilnidipine)



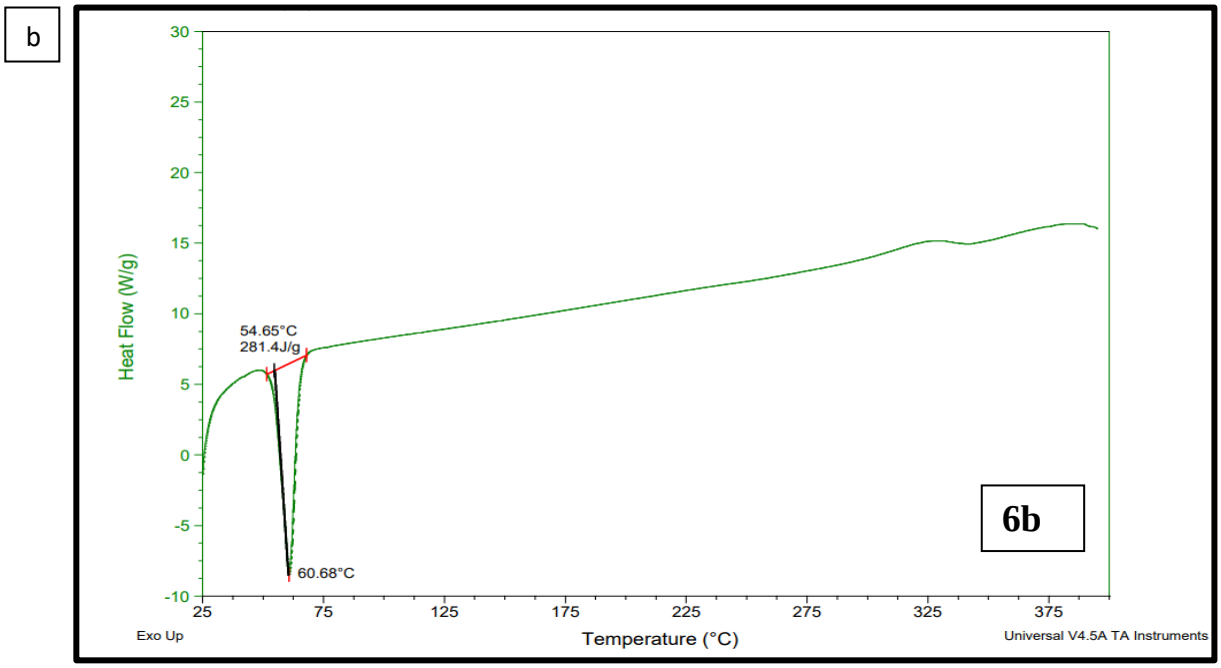


Figure 6a. DSC of Pure Cilnidipine b) DSC of Optimized batch of solid dispersion

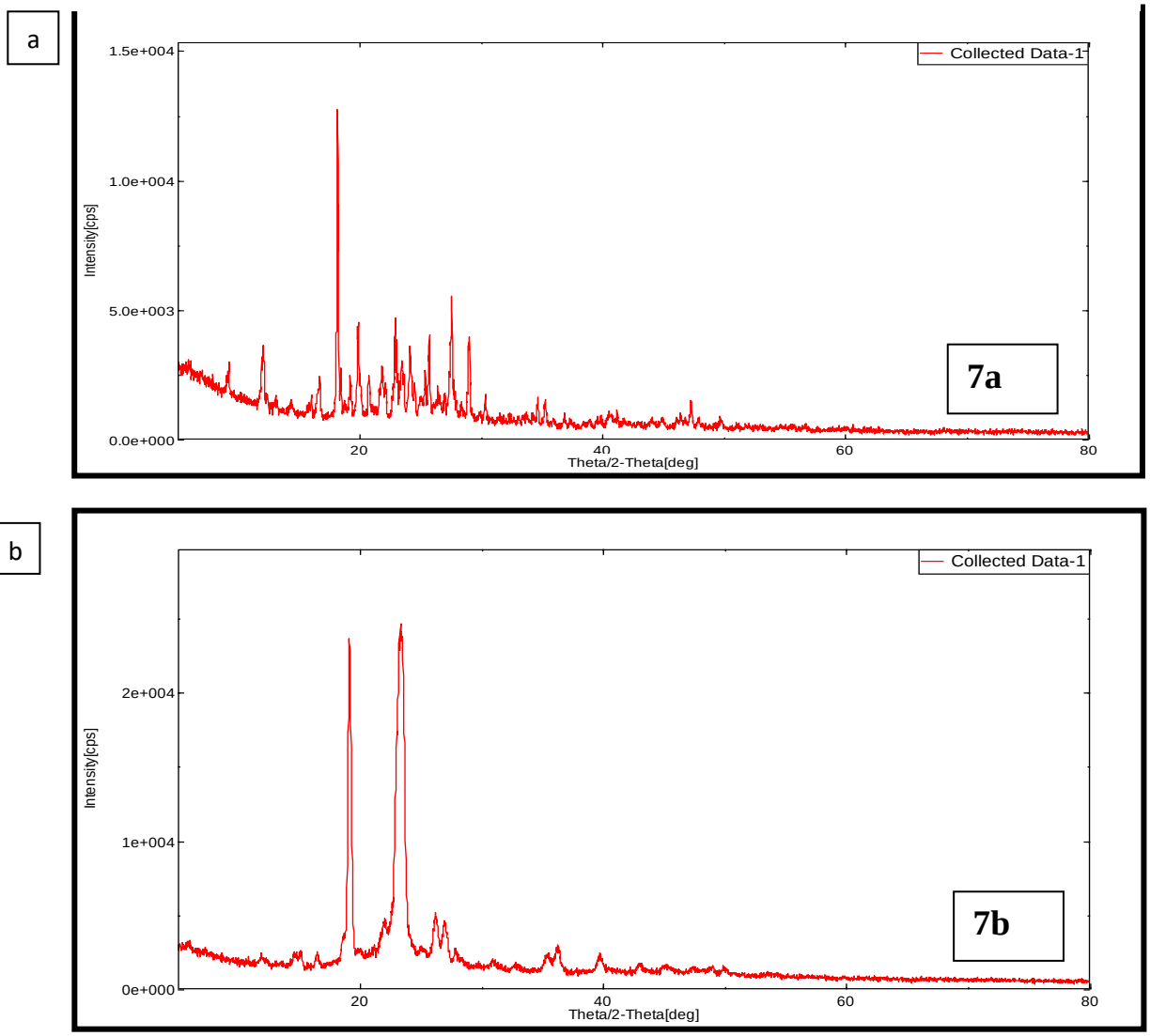


Figure 7a. XRD of Pure Cilnidipine b) XRD of Optimized solid dispersion of Cilnidipine

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batches as well as the dissolution profile study of solid dispersions Solvent evaporation method was concluded as the optimised method and batch F6 with was ratio of 1:9 (Cilnidipine: Poloxamer 188) was concluded as optimized batch.

Conclusion

In the current work, solid dispersion with Poloxamer 188 was used in a 1:9 ratio with solvent evaporation to improve the solubility and dissolving characteristics of cilnidipine. The results of the study demonstrated that a solid dispersion of cilnidipine could be successfully prepared using a 1:9 ratio of Poloxamer 188 and solvent evaporation. The dissolution characteristics of the solid dispersion were significantly improved, with a dissolution rate of 98.55% at 60 minutes. The solid-state characterization techniques, such as X-ray diffraction (XRD) and differential scanning calorimetry (DSC), confirmed that the enhancement in dissolution was attributed to the conversion of cilnidipine from its crystalline form to a less crystalline and possibly amorphous form. These findings suggest that this approach effectively improves the dissolution behaviour of cilnidipine, which may have implications for its oral bioavailability.

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Conflict of interest

The authors declare that there is no conflict of interest.

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