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Beni-Suef Univ J Basic Appl Sci (2022) 11:83
https://doi.org/10.1186/s43088-022-00259-3

Beni-Suef University Journal of Basic and Applied Sciences

RESEARCH Open Access

Development and characterization of solid dispersion-based orodispersible tablets of cilnidipine

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Abstract

Background: Cilnidipine, a calcium channel blocker, is the first-line drug for hypertension and belongs to Biopharmaceutics Classification System II. To mitigate its extensive first-pass metabolism and improve patient compliance, the present study was performed to develop and characterize solid dispersion-based orodispersible tablets.

Results: The phase solubility study with polyvinyl pyrrolidone 15% has shown a 140-fold increase in solubility. X-ray diffraction and differential scanning calorimetry studies emphasized the conversion of solid dispersion from crystalline to amorphous state. Solid dispersion 3 resulted in 142-fold improvement in solubility, 96% of drug content, and percentage drug release was 71.9% at 60 min. F11 containing crospovidone (10 mg) and sodium starch glycolate (16 mg) in combination at higher concentration as super-disintegrants showed the least disintegration time of 26.6 s. In vitro dissolution results are subjected to statistical analysis and found that the formulation (F11) has shown an increased dissolution rate (88.62% at 10 min), compared to the marketed formulation (83% at 60 min).

Conclusions: Solid dispersion prepared by a solvent evaporation method using PVP as a carrier can be utilized for enhancing the solubility of cilnidipine. The incorporation of super-disintegrants in combination improves the dissolution rate of orodispersible tablets. Further, the study can be substantiated by performing stability and in vivo studies in the future.

Keywords: Cilnidipine, Orodispersible tablets, PVP, Solid dispersion, Solvent evaporation method, Super-disintegrants

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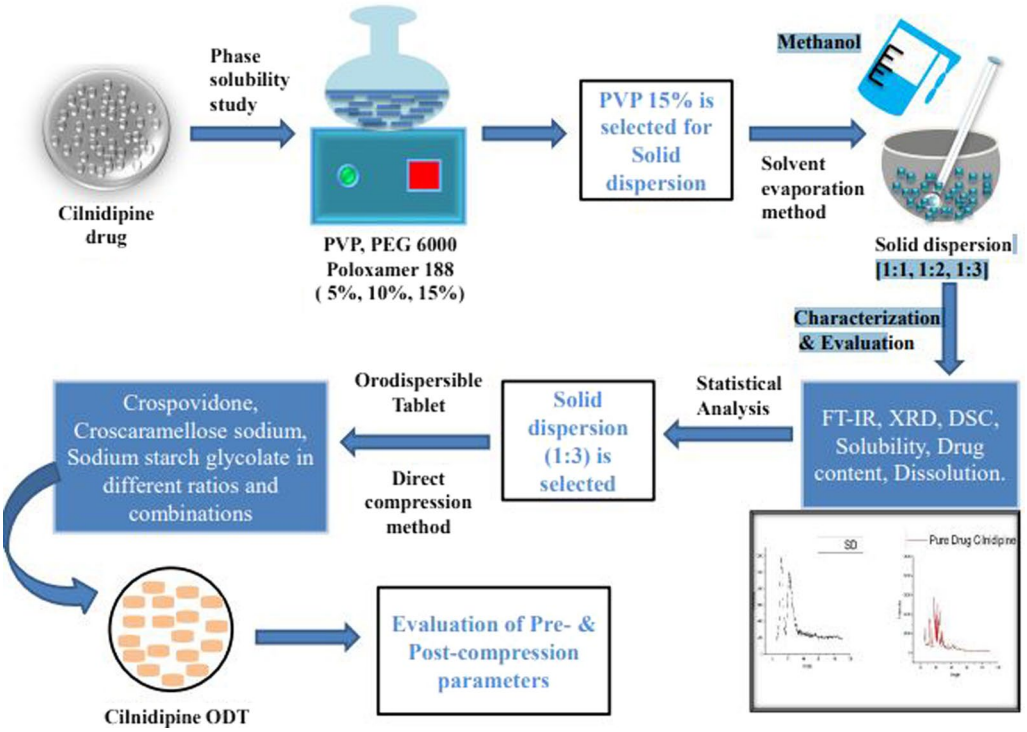
Graphical Abstract



1 Background

Hypertension is a chronic medical condition in which the blood pressure is elevated above the normal range (120/80 mmHg). It is the most important risk factor which acts as a sign of multiple physiological abnormalities [1]. One of the most widely used antihypertensive agents is calcium channel blockers. Cilnidipine is a 4th generation dihydropyridine calcium antagonist. It exhibits both L- and N-type calcium channel blocking activity [2]. L-type calcium channels are distributed in the smooth muscles and N-type in the brain. It has been clinically demonstrated to be effective for morning hypertension and it does not exert effects on pedal edema. It controls proteinuria and causes less reflex tachycardia compared to other calcium channel blockers. It also inhibits sympathetic neurotransmitter release and controls the blood pressure [3]. Therefore, the treatment of hypertension with cilnidipine minimizes the development of renal, cardiovascular and cerebrovascular diseases [4, 5]. Cilnidipine is a biopharmaceutics classification II drug that possesses low solubility and high permeability. It undergoes extensive first-pass metabolism [6, 7]. It is available as conventional tablet form in the market to treat hypertension and its associated disorders. Based on the patient conditions and physicochemical characteristics of the drug, orodispersible formulation serves as a convenient method of administration without need of water. The patient conditions include dysphagia, stroke, bedridden, and psychiatric patients. The formulation releases the drug in mouth for absorption through pre-gastric, gastric, and post-gastric segments. This kind of absorption results in faster onset of action and improved bioavailability which leads to better clinical performance [8]. Orodispersible tablets is defined as an oral solid dosage form containing super-disintegrants as a major component to enhance the disintegrating and dissolution property of the drug. As per Indian Pharmacopoeia, the orodispersible tablets must disintegrate within 3 min. The formulation gets dispersed in the saliva without the need of water and leads to faster disintegration which produces quick onset of action. The drugs that extensively undergo first-pass metabolism can be reduced when formulated as orodispersible tablets [9]. This is due to the pre-gastric absorption of drug from the mouth. It causes a higher level of disintegration by undergoing mechanisms such as swelling, wicking, deformation, and particle repulsive forces [10].

Orodispersible tablets are prepared by various methods such as direct compression, molding, lyophilization, sublimation, spray drying, mass extrusion, phase transition, nanonization, and cotton candy process [11, 12]. The essential criteria for developing orodispersible tablets is solubility of the drug. To enhance the solubility of poorly soluble drugs, it is subjected to a solid dispersion (SD) technique which is defined as the dispersion of API in a carrier that causes physical modification and thereby increases its solubility. The SD process has emerged as a most productive method of improving poorly water-soluble drugs. The selection of carriers plays a critical role in the properties of SD that promotes drug dissolution and stabilization. Carriers commonly employed are amorphous, crystalline, or semicrystalline in nature. Formulation-related and process-related parameters should be considered for choosing the appropriate carrier [13, 14]. SD are categorized into four types based on the forms of the carrier used. They are first, second, third, and fourth generation SDs. The techniques used in the preparation of SD are solvent-based methods such as solvent evaporation, spray drying, and rotating jet spinning and fusion-based methods include melt extrusion, melt granulation, kinetisol, etc. SD is a traditional method that is highly reproducible and cost-effective. This technique offers rapid dissolution which increases the rate and extent of drug absorption [15, 16]. Due to the poor solubility nature of cilnidipine, solid dispersion is performed to enhance it and formulated as an orodispersible tablet with super-disintegrants to achieve faster onset of action which provides effective drug delivery bypassing first-pass metabolism and may improve patient compliance. The main aim of the study was to develop and characterize solid dispersion-based orodispersible tablets of cilnidipine. The objective of the research work was to prepare cilnidipine solid dispersion using PVP from phase solubility studies in different ratios. Based on the evaluation and characterization, the solid dispersion that exhibited high solubility and in vitro dissolution profile was formulated into an orodispersible tablet using different super-disintegrants in combination and alone. The formulated tablets are evaluated and its dissolution profiles are compared with the conventional marketed tablet.

2 Materials and methods

2.1 Materials

Cilnidipine (Ordain Health Care Global Pvt Ltd, Kanchipuram, Tamil Nadu, India), Polyvinyl pyrrolidone, Polyethylene glycol 6000, Sodium starch glycolate, Mannitol, Microcrystalline cellulose, and Magnesium stearate (Loba Chemie Pvt Ltd, Mumbai, India), Poloxamer 188, Crospovidone and Croscarmellose sodium (Yarrow Chem products, Mumbai, India), Aerosil (Otto chemicals, Mumbai, India).

2.2 Methods

2.2.1 Phase solubility study of the carrier

The Shake flask method is used to determine the solubilizing nature of the carrier. Aqueous solutions of different carriers such as polyvinyl pyrrolidone, polyethylene glycol 6000, and Poloxamer 188 were prepared in different concentrations (5%, 10%, 15%). To these solutions, an excess quantity of drug was added until the formation of saturated solution. Samples were placed in an Orbital shaker for 24 h at 60 rpm and centrifuged for 10 min at 3000 rpm. The supernatant was diluted and analyzed using a UV–visible double beam spectrophotometer (UV 1650 PC, Shimadzu Corporation, Japan) at 242 nm [17].

2.2.2 Preparation of physical mixture

The physical mixtures were prepared using drug and carrier in different ratios. The required quantity of drug and carrier was triturated for 5 min in a glass mortar and pestle. The mixture was packed and stored in a desiccator [18].

2.2.3 Preparation of solid dispersion

The polymer which exhibits maximum solubility in phase solubility study was selected to prepare solid dispersion in different ratios by solvent evaporation method. Methanol was used as a solvent. Drug and carrier solutions were prepared separately by dissolving an accurately weighed amount of them in a specified quantity of solvent. Both the mixtures were mixed together and kept aside until the solvent gets evaporated at room temperature. The final product was ground to powder using mortar and pestle, passed through sieve no #44, packed, and stored in a desiccator [19] (Table 1).

2.3 Characterization of solid dispersion

2.3.1 Fourier transform infrared spectroscopy

Fourier transform infrared (FT-IR) spectra were obtained by using a Shimadzu Fourier transform infrared spectrophotometer 8400 S, Japan. The samples were prepared by KBr pellet method using KBr press model M 15

Table 1 Ratio for physical mixture and solid dispersion

Quantity of drug (mg)	Quantity of carrier (mg)	Ratio (drug:carrier)
200	200	1:1
200	400	1:2
200	600	1:3

instrument. The scanning range used was 500–4000/cm and the resolution was 2/cm.

2.3.2 X-ray diffraction study

The X-ray diffraction (XRD) study was carried out for the solid dispersion prepared using PVP in 1:3 ratio. Empyrean, Malvern Panalytical multipurpose diffractometer with MultiCore Optics (United Kingdom) was used to obtain diffractogram. The samples were analyzed in the angle range of 0–100°. The crystallinity index was determined using the formula.

$$\text{Crystallinity index} = \text{Area of all crystalline peaks} \div \text{Area of crystalline and amorphous peaks} \times 100.$$

2.3.3 Differential scanning calorimetry

The differential scanning calorimetry (DSC) measurements were performed using a Mettler Toledo Differential scanning calorimeter instrument, Mumbai, India. 6–7 mg of sample were heated under nitrogen gas in sealed aluminum pans over a temperature range of 100–150 °C and the thermograms were recorded at a heating rate of 40 °C/min.

2.4 Evaluation of solid dispersion

2.4.1 Solubility study of the physical mixture and solid dispersion

The solubility study of the physical mixture and solid dispersion was performed in solvents such as water and citrophosphate buffer pH 6.8 with SLS 0.2%. The shake flask method is employed. The prepared solid dispersion was added to 10 ml of water and 10 ml of citrophosphate buffer pH 6.8 with SLS 0.2% separately. An excess quantity of the samples (PM and SD) was added to these solutions until the sample settles in the bottom. The samples were placed in an orbital shaker for 24 h at 60 rpm and centrifuged for 10 min at 3000 rpm. The filtrates were diluted and the solubility was determined by measuring the absorbance using a UV–visible double beam spectrophotometer (UV 1650 PC, Shimadzu Corporation, Japan) at 242 nm [17].

2.4.2 Drug content

Drug content of solid dispersion was evaluated by dissolving an amount of solid dispersion equivalent to 10 mg of cilnidipine in 10 ml of citrophosphate buffer pH 6.8 with SLS 0.2%. The stock solution was diluted appropriately and analyzed using a UV–visible double beam spectrophotometer (UV 1650 PC, Shimadzu Corporation, Japan) at 242 nm.

2.4.3 In vitro dissolution studies

In vitro dissolution studies were carried out using USP Type 1 dissolution apparatus, Basket type (Lab India DS 8000, Maharashtra, India), rotating at 50 rpm. The dissolution medium used was citrophosphate buffer pH 6.8 with SLS 0.2% (900 ml) maintained at 37 ± 0.5 °C. The samples were withdrawn at certain time intervals and the sink condition was maintained by replacing same volume of buffer. Then, it was filtered, and analyzed at 242 nm using citrophosphate buffer pH 6.8 with SLS 0.2% as a blank. All the values are statistically analyzed to identify the formulation that produces best results.

2.5 Formulation of orodispersible tablet

The optimized solid dispersion was formulated into an orodispersible tablet by direct compression method. The tablet formulation consists of solid dispersion, super-disintegrants, and other excipients. Crospovidone (CP), croscarmellose (CC), and sodium starch glycolate (SSG) were used as super-disintegrants in different concentrations and combinations. Mannitol was added for producing a cooling effect and it also functions as diluent and sweetener. All the ingredients were triturated well by geometric mixing and passed through sieve no #60. The powder was compressed into a tablet by a single punch tablet machine (Rimek, Ahmedabad, India) (Table 2).

2.6 Evaluation of powder

2.6.1 Pre-compression parameters

The powder was evaluated for flow properties such as bulk density, tapped density, Hausner ratio, compressibility index, and angle of repose [20].

2.7 Evaluation of tablets

2.7.1 Post-compression parameters

The tablet was evaluated for post-compression parameters such as hardness, friability, drug content, disintegration studies, and *in vitro* dissolution studies [20].

2.7.2 Disintegration studies

The disintegration of the tablet was measured using the USP disintegration apparatus (Lab India DT 1000, Maharashtra). The medium used was citrophosphate buffer pH 6.8 with SLS 0.2%. The time taken for the cilnidipine orodispersible tablet to disintegrate was noted.

2.7.3 In vitro dissolution studies

In vitro dissolution studies were carried out using USP Type 2 dissolution apparatus, Paddle type (Lab India DS 8000, Maharashtra, India), rotating at 50 rpm. The dissolution medium used was citrophosphate buffer pH 6.8 with SLS 0.2% (900 ml) maintained at 37 ± 0.5 °C. The

Table 2 Formulation of cilnidipine orodispersible tablets

Formulations	Ingredients (mg)							
	SD	CP	CS	SSG	Mannitol	MCC	Aerosil	Mg stearate
F1	40	4	–	–	113	40	1	2
F2	40	–	2	–	115	40	1	2
F3	40	–	–	4	113	40	1	2
F4	40	4	2	–	111	40	1	2
F5	40	4	–	4	109	40	1	2
F6	40	–	2	4	111	40	1	2
F7	40	10	–	–	107	40	1	2
F8	40	–	10	–	107	40	1	2
F9	40	–	–	16	101	40	1	2
F10	40	10	10	–	97	40	1	2
F11	40	10	–	16	91	40	1	2
F12	40	–	10	16	91	40	1	2

SD Solid dispersion, *CP* Crospovidone, *CS* Croscarmellose, *SSG* Sodium starch glycolate, *MCC* Microcrystalline cellulose, *Mg stearate* Magnesium stearate

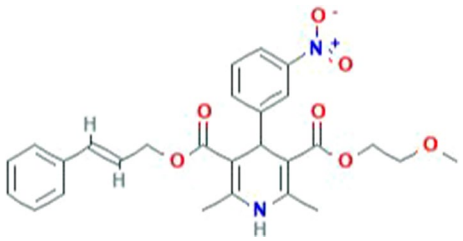


Fig. 1 The chemical structure of the drug cilnidipine

samples were withdrawn at certain time intervals and the sink condition was maintained by replacing same volume of buffer. Then, it was filtered, and analyzed at 242 nm using citrophosphate buffer pH 6.8 with SLS 0.2% as a blank. Drug concentration was calculated from the calibration curve and expressed as percentage of drug dissolved. All the formulations were compared with the marketed cilnidipine tablets for release profile.

2.7.4 Statistical analysis

Statistical analysis of the in vitro dissolution data between orodispersible formulations (F1–F12) and marketed tablet was assessed by difference factor (f1) similarity factor (f2) using DD Solver. The obtained value for the data is compared to determine the statistical significance and select the best formulation. The f2 value greater than 50, i.e., (50–100) ensures the sameness and the value less than 50 indicates non-similarity between the two dissolution profiles. The f1 value less than 15, i.e., (0–15) ensures the equivalence of two profiles, the value increases when two profiles become less similar [21, 22] (Figs. 1, 2).

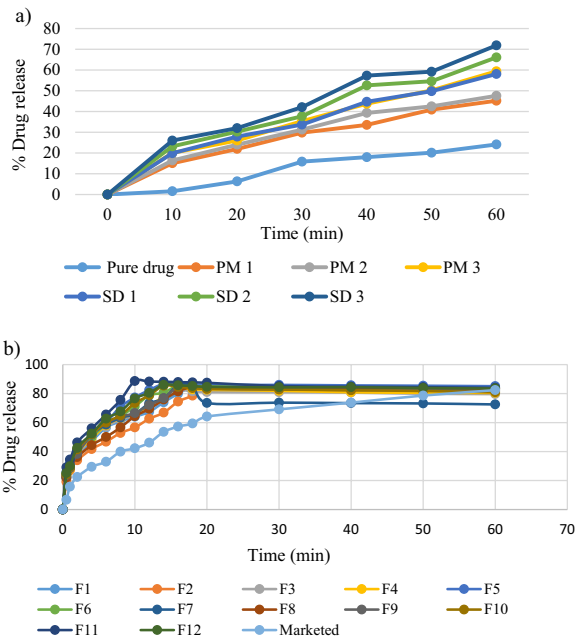


Fig. 2 **a** Dissolution studies of PM and SD. The graph represents a comparative dissolution profile between pure drug, PM and SD. **b** Dissolution studies of marketed and formulated orodispersible tablets. The graph represents a comparative dissolution profile between the conventional marketed formulation and formulated orodispersible tablets

3 Result

3.1 Phase solubility study of carrier

The pure drug has a solubility of 0.0071 mg/ml in water and 0.2734 mg/ml in citrophosphate buffer pH 6.8 with SLS 0.2%. The phase solubility study of drug with

Table 3 Phase solubility study of drug with aqueous solution of carrier

Carrier	5% (mg/ml)	Inference	10% (mg/ml)	Inference	15% (mg/ml)	Inference
PVP	0.3805	Very slightly soluble	0.6722	Very slightly soluble	0.9976	Very slightly soluble
PEG 6000	0.0463	Practically insoluble	0.0876	Practically insoluble	0.1076	Very slightly soluble
Poloxamer 188	0.0638	Practically insoluble	0.1277	Very slightly soluble	0.2491	Very slightly soluble

Table 4 FT-IR result [23]

S. no.	Functional group	Reported frequency (cm^{-1})	Frequency of drug (cm^{-1})	Frequency of SD (cm^{-1})	Frequency of drug and excipients (cm^{-1})
1	C–N aromatic 2° amine	1020–1250	1119.71	1103.32	1104.28
2	N–O	1360–1550	1389.76	1380.11	1373.36
3	C=O	1630–1980	1752.42	1746.60	1635.69
4	–OCH3	2815–2950	2929.97	2923.22	2917.43
5	C–O	1200–1225	1225.80	1232.55	1249.91
6	N–H Aromatic 2° amine	3250–3500	3464.27	3396.76	3416.05

SD solid dispersion

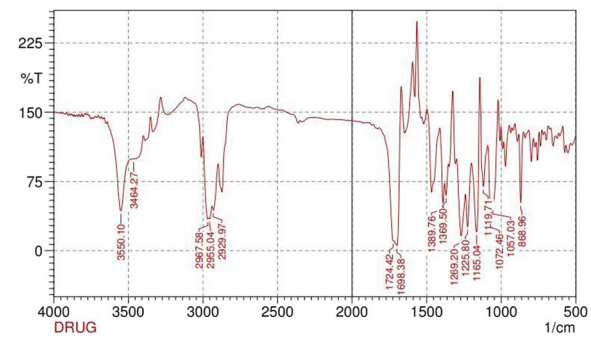


Fig. 3 Fourier transform infrared spectroscopy report of cilnidipine. The peak positions of cilnidipine are represented in wave numbers

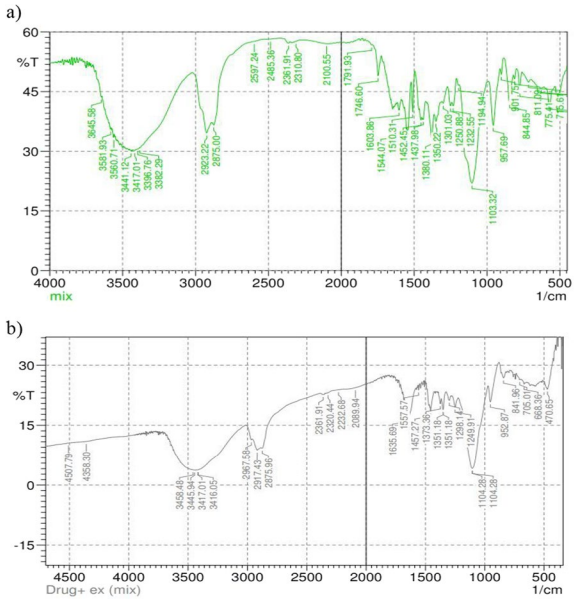


Fig. 4 **a** Fourier transform infrared spectroscopy report of solid dispersion. **b** Fourier transform infrared spectroscopy report of drug–excipient mixture. The peak positions of cilnidipine are depicted in wave numbers

aqueous solution of carrier such as PVP, PEG 6000, and Poloxamer 188 is described in Table 3.

3.2 Characterization of solid dispersion

3.2.1 Fourier transform infrared spectroscopy

The drug–excipient compatibility was determined by comparing the spectra of pure drug, solid dispersion, and drug–excipient mixture. The functional group and frequencies of drug, excipient mixture, and SD are reported in Table 4 and Figs. 3 and 4.

3.2.2 X-ray diffraction study

The percent crystallinity is determined by calculating the area of the crystalline and amorphous peaks using the Origin pro software. The crystallinity index for pure drug and solid dispersion was found to be 78.75% and 15.71%, respectively. Area of crystalline and amorphous peaks are tabulated in Table 5 and Fig. 5.

3.2.3 Differential scanning calorimetry

It was observed that the endothermic peak is shifted from 112.01 to 116.74 °C in SD. And PVP has not shown any fusion peak due to its amorphous nature. The onset

Table 5 XRD result

Contents	Pure drug	Solid dispersion
No. of peaks	22	02
Area of crystalline peaks	35,415.26	2340.96
Area of crystalline and amorphous peaks	44,971.01	14,893.65
Crystallinity index	78.75%	15.71%

Table 6 DSC result

Samples	Peak area (mJ)	Enthalpy change (Jg)	Peak (°C)	Glass transition (°C)
Drug	559.11	93.18	112.01	–
PVP	–	–	–	128.12
SD	1533.14	255.52	116.74	–

of peak, peak area, enthalpy change and glass transition temperature of drug, PVP, and SD are described in Table 6 and Fig. 6.

3.3 Evaluation of solid dispersion

Based on the phase solubility studies, it was evident that PVP has shown maximum solubility. Therefore, the solid dispersions were prepared using PVP as carrier in the ratios of 1:1, 1:2, and 1:3.

3.3.1 Solubility study of the physical mixture and solid dispersion

The solubility values of physical mixture and solid dispersion are listed in Table 3.

3.3.2 Drug content

The obtained absorbance for the drug content value was correlated with the standard graph. It was found to be in the range of 95–96% for cilnidipine solid dispersions.

3.3.3 In vitro dissolution studies

The % drug release for pure drug was 24.13% after 60 min. The % drug release for SD1, SD2, and SD3 was found to be 58.1%, 66.1%, and 71.9%, respectively, at 60 min. The dissolution profiles of cilnidipine, PM, and SD are represented in Fig. 2.

3.3.4 Statistical analysis

Experimental values of dissolution studies were analyzed by comparison between solid dispersions (SD1, SD2, SD3) and pure drug to evaluate the variance and best formulation. The f1 and f2 value obtained by comparing SDs as test product and pure drug as reference product are 171.96, 207.27, 235.15 and 31.43, 27.29, 24.54, respectively. The values are tabulated in Tables 7 and 8.

3.4 Evaluation of powder

3.4.1 Pre-compression parameters

The powder was evaluated for flow properties such as bulk density, tapped density, Hausner ratio,

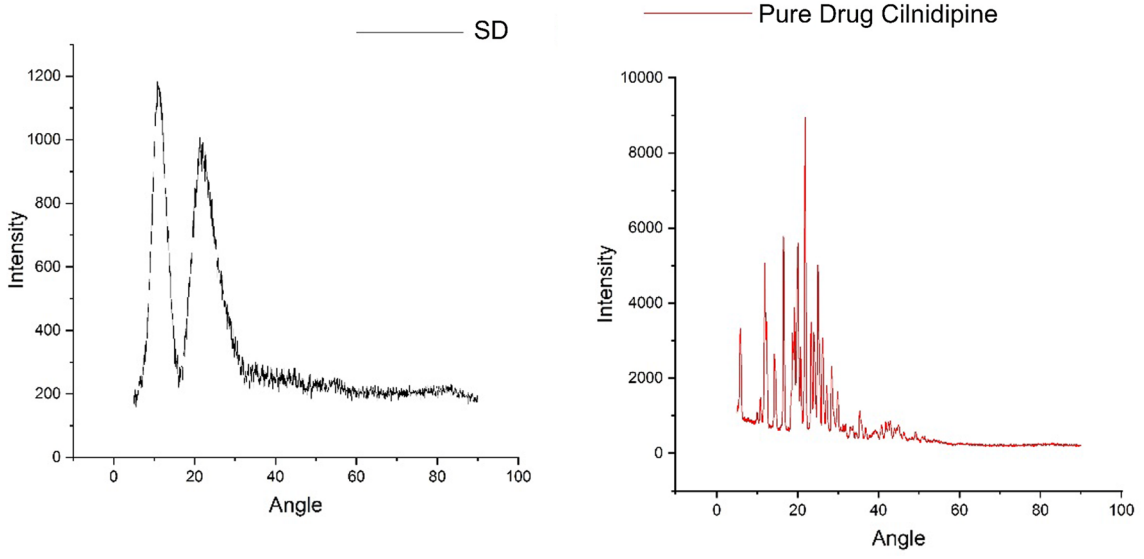


Fig. 5 XRD pattern of solid dispersion and pure cilnidipine. The presence of sharp peaks in cilnidipine indicates the crystalline nature and the scattered lines in the solid dispersion indicate the amorphous nature

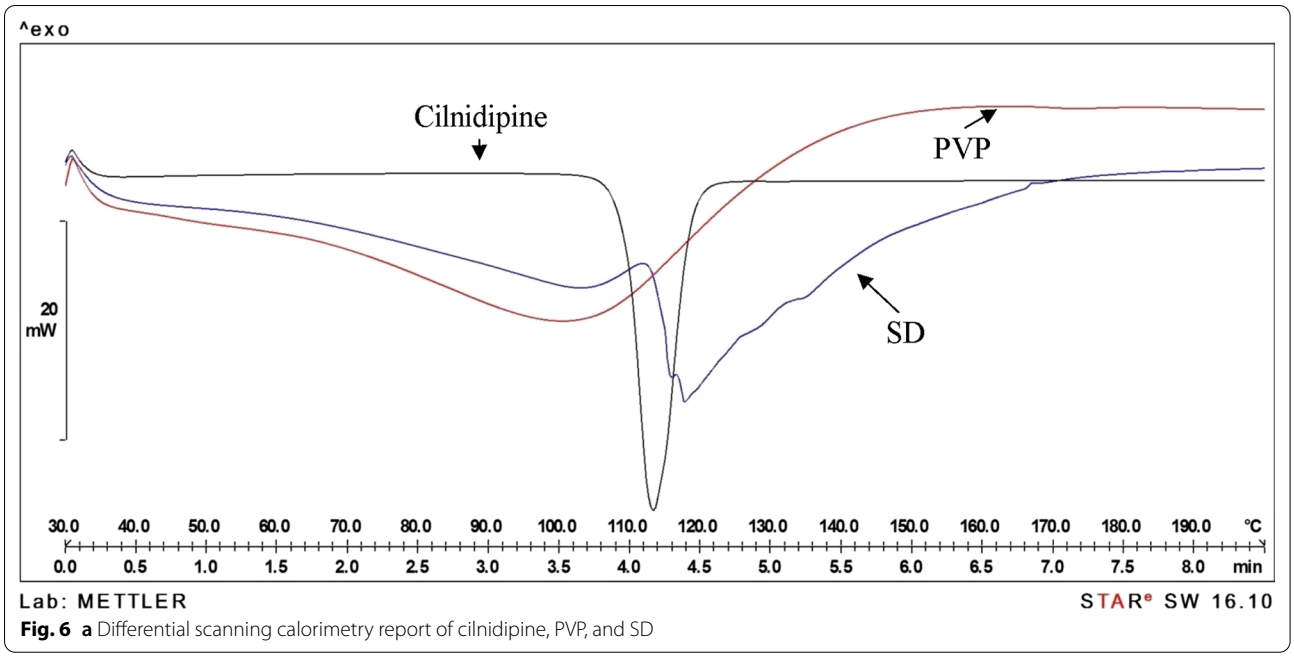


Fig. 6 **a** Differential scanning calorimetry report of cilnidipine, PVP, and SD

Table 7 Solubility study of solid dispersion (SD) and physical mixture (PM)

Formulation	Buffer (mcg/ml)	Inference	Water (mcg/ml)	Inference
Pure drug	0.2734	Very slightly soluble	0.0071	Practically insoluble
SD1	0.6546	Very slightly soluble	0.4832	Very slightly soluble
SD2	0.8424	Very slightly soluble	0.5570	Very slightly soluble
SD3	1.0051	Slightly soluble	0.6371	Very slightly soluble
PM1	0.4506	Very slightly soluble	0.3154	Very slightly soluble
PM2	0.5996	Very slightly soluble	0.4318	Very slightly soluble
PM3	0.7685	Very slightly soluble	0.5157	Very slightly soluble

Table 8 Difference factor (f1) and similarity factor (f2) values for SD

SD	f1	f2
SD 1	171.96	31.43
SD 2	207.27	27.29
SD 3	235.15	24.54

compressibility index, and angle of repose [20]. The values are summarized in Table 9.

3.5 Evaluation of tablets

3.5.1 Post-compression parameters

The post-compression parameters for the prepared tablet such as hardness, friability, drug content values [20] are described in Table 10.

3.5.2 Disintegration studies

The disintegration time for all the formulations was found to be in the range of 26.6 to 42.6 s. The values are summarized in Table 10.

3.5.3 In vitro dissolution studies

In vitro dissolution studies for the formulations (F1–F11) were found to be in the range of 21.52–64.02%, 19.15–56.6%, 22.32–64.81%, 23–66.17%, 25.83–77.28%, 24.58–71.17%, 22.43–66.06%, 21.87–64.36%, 23.68–66.51%, 24.25–73.43%, 29.12–88.62% and 25.15–76.6%, respectively. The dissolution profiles of orodispersible tablets and conventional marketed formulations are represented in Fig. 2.

3.5.4 Statistical analysis

Experimental values of dissolution studies were analyzed by comparison between orodispersible formulations

Table 9 Pre-compression parameters

Formulations	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's index (%)	Angle of repose
F1	0.31 ± 0	0.32 ± 0	1.03 ± 0	3.10 ± 0	32.95 ± 1.29
F2	0.31 ± 0.01	0.32 ± 0.007	1.03 ± 0	3.05 ± 0.03	33.36 ± 1.54
F3	0.30 ± 0.01	0.32 ± 0	1.04 ± 0.01	3.03 ± 2.44	35.31 ± 0.47
F4	0.30 ± 0.01	0.32 ± 0.007	1.05 ± 0.01	5.13 ± 1.44	33.97 ± 1.46
F5	0.32 ± 0.007	0.34 ± 0.01	1.05 ± 0.01	4.87 ± 1.30	33.16 ± 1.14
F6	0.31 ± 0.007	0.32 ± 0.01	1.04 ± 0.01	4.06 ± 1.41	34.0 ± 1.42
F7	0.30 ± 0.01	0.32 ± 0.007	1.05 ± 0.01	5.13 ± 1.44	34.29 ± 1.25
F8	0.31 ± 0.007	0.33 ± 0	1.05 ± 0.01	5.05 ± 1.42	32.21 ± 0.26
F9	0.30 ± 0.007	0.31 ± 0.01	1.04 ± 0.01	4.19 ± 1.45	34.45 ± 1.8
F10	0.31 ± 0.01	0.32 ± 0.01	1.05 ± 0.01	5.11 ± 1.47	32.24 ± 0.24
F11	0.31 ± 0.007	0.32 ± 0.007	1.03 ± 0	3.07 ± 0.03	33.49 ± 1.72
F12	0.32 ± 0.007	0.33 ± 0	1.03 ± 0	3.0 ± 0.04	32.13 ± 0.30

Mean ± standard deviation, n = 3

Table 10 Post-compression parameters

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (Newton)	Friability (%)	Drug content (%)	Disintegration time (s)
F1	0.19 ± 0.01	1.3 ± 0.1	33.0 ± 1.73	0.38 ± 0.03	92.1 ± 0.78	42.0 ± 2.16
F2	0.20 ± 0.01	1.2 ± 0.1	32.6 ± 1.15	0.24 ± 0.06	93.6 ± 0.16	42.3 ± 2.05
F3	0.20 ± 0	1.2 ± 0.1	29.6 ± 1.52	0.38 ± 0.10	92.4 ± 0.32	42.6 ± 1.24
F4	0.20 ± 0.01	1.2 ± 0.1	33.6 ± 0.58	0.49 ± 0.13	91.4 ± 0.36	40.3 ± 0.94
F5	0.20 ± 0.01	1.1 ± 0.1	31.3 ± 1.15	0.38 ± 0.17	93.2 ± 0.20	32.0 ± 1.63
F6	0.19 ± 0.007	1.3 ± 0	32.3 ± 0.57	0.35 ± 0.21	92.4 ± 0.09	40.3 ± 1.24
F7	0.35 ± 0.01	1.1 ± 0.1	30.6 ± 0.58	0.35 ± 0.03	92.7 ± 0.16	40.3 ± 0.47
F8	0.20 ± 0.01	1.3 ± 0.1	33.0 ± 1.73	0.38 ± 0.10	92.3 ± 0.12	42.6 ± 1.24
F9	0.19 ± 0.007	1.2 ± 0	31.3 ± 0.57	0.27 ± 0.03	92.1 ± 0.14	36.3 ± 1.24
F10	0.20 ± 0	1.2 ± 0.1	31.0 ± 1.0	0.35 ± 0.14	93.4 ± 0.32	32.6 ± 0.47
F11	0.19 ± 0.01	1.3 ± 0	32.0 ± 0	0.33 ± 0.13	93.3 ± 0.12	26.6 ± 1.24
F12	0.19 ± 0.01	1.1 ± 0.1	32.3 ± 0.57	0.27 ± 0.08	93.4 ± 0.09	32.0 ± 0

Mean ± standard deviation, n = 3

(F1–F12) and marketed tablet to evaluate the variance and best formulation. The f1 and f2 values obtained by comparing orodispersible formulations as test product and marketed tablet as reference product are in the range of 26.49–51.64 and 28.51–43.88, respectively. All the values are tabulated in Table 11.

4 Discussion

In the phase solubility studies of cilnidipine, the solubility was found to increase as the concentration of the carrier increases. Maximum enhancement in solubility was manifested by 15% PVP. It has shown 140-fold increase in the solubility of the drug. Mallesh kurakula et al. [24] reported that the PVP, water-soluble amorphous polymer exhibits high solubility when dispersed with a poorly water-soluble drugs and the magnitude of solubility

Table 11 Difference factor (f1) and similarity factor (f2) values for orodispersible tablets

Formulation code	f1	f2
F 01	35.03	37.73
F 02	26.49	43.88
F 03	34.41	37.59
F 04	36.07	36.50
F 05	45.56	31.61
F 06	40.43	34.00
F 07	35.72	36.29
F 08	33.42	38.48
F 09	37.63	35.68
F 10	41.13	33.49
F 11	51.64	28.51
F 12	44.08	32.13

depends on the molecular weight and concentration of the PVP. Therefore, PVP was found to be the best carrier which may be due to its superior solubility profile and hydrogen bonding with the drug as reported in many studies [14].

The FT-IR results exhibited that the samples retained the drug's specific functional peak at frequencies such as 1020–1250, 1360–1550, 1630–1980, 2815–2950, 1200–1225, and 3250–3500 cm^{-1} indicating the absence of drug–excipient interaction.

The presence of various sharp peaks in different angles of XRD pattern for the pure drug indicates the crystalline nature of the drug. The diffractogram of solid dispersion (SD3) exhibits a fewer number of peaks and broad diffraction pattern which indicates the amorphous character. Therefore, the absence of sharp peaks, reduction of intensity in existing peaks, and reduction in the crystallinity value confirm the conversion of crystalline to amorphous nature of the drug [25].

The obtained thermogram of differential scanning calorimetry studies for the solid dispersion revealed that the drug peak was disappeared from the formulation, indicating the amorphization of the drug.

Solubility study of the physical mixture and solid dispersion resulted in enhancement of solubility in both citrophosphate buffer pH 6.8 with SLS 0.2% and water. SD3 has been considered as the optimized batch as it exhibited high solubility compared with the other batches (142-fold improvement). The increase in the solubility may be attributed to the presence of higher carrier concentration, inhibition of crystallization process, increase in surface area, and wettability of the drug resulting in formation of amorphous solid dispersion [26, 27].

The drug content of solid dispersions was found to be within the range as mentioned in the Indian Pharmacopoeia for cilnidipine tablets (Not less than 90% and not more than 110%).

The dissolution enhancing property of PVP plays a significant role in the physical mixture and solid dispersion. SD3 acquired a greater dissolution rate due to the higher carrier content in the dispersion and selected for the formulation development.

The f1 values more than 15 and f2 values less than 50 denote that the profiles are not similar. The f1 and f2 values of all the preparations complies as per the recommendations and confirm that their dissolution profiles are different from pure drug. Therefore, f1 and f2 values of SD3 (235.15 and 24.54) were considered to be the best preparation for formulating into orodispersible tablets.

Further, the result of the powder flow properties connotes the excellent compressibility and good flow behavior. A slight increase in angle of repose of the powder blend can be associated with high amount of mannitol. The addition of microcrystalline cellulose accounts to excellent compressibility of the blend despite large quantity of mannitol [28].

The post-compression parameters for the prepared tablet such as weight variation, thickness, hardness, and friability were found to be within the acceptable range and comply with the Indian Pharmacopoeia standard.

As suggested in the IP standard, all the formulations comply with the requirement of disintegration time. The fastest disintegration time was 26.6 s for formulation F11, which contains crospovidone and sodium starch glycolate in combination at the highest concentration. The combined effect of wicking and swelling of CP and SSG might have resulted in faster disintegration of the orodispersible tablets [29, 30]. Hence, it has been concluded that the combination of super-disintegrants may significantly influence the disintegration time than when they are used alone.

The in vitro percentage drug release of all the formulations and the marketed tablets were within the acceptable range as per IP specifications [29, 30]. The study results suggest that the presence of two disintegrants has shown maximum drug release within a short period of time than a single super-disintegrant. Formulations containing single super-disintegrants have taken nearly 15–20 min to show maximum drug release. A comparative study has been conducted between optimized formulation (F11) and conventional marketed formulation. It has been observed that the F11 containing crospovidone and sodium starch glycolate in combination at the highest concentration exhibited maximum drug release of 88.62% at 10 min while conventional marketed tablet showed 82.38% at the end of 60 min. So, F11 was considered as the best formulation.

The f1 value more than 15 and f2 value less than 50 denotes that the profiles are not similar. The f1 and f2 values of all the formulations comply as per the recommendations and confirm that their dissolution profiles are different from marketed dosage form. Therefore, f1 and f2 values (51.54 and 28.5) for F11 were selected and found to be the best among others.

The solid dispersion technique is one of the most efficacious commercially scalable method for improving the solubility of the poorly water-soluble drugs. The major concern related to the storage conditions in the preparation of solid dispersion affects its crystallinity which shows a drastic change in the dissolution behavior of the drug. Therefore, solid dispersion needs to be maintained at a suitable condition for further use. The prepared solid dispersion must be subjected to stability studies. The orodispersible tablet serves as a convenient oral solid dosage form for the wide populations. Few limitations include, those drugs that have

obnoxious taste cannot be formulated and also inadequate mechanical strength of the orodispersible tablets may require specialized product packaging during transportation. The future perspective of the present work involves execution of in vivo studies for the optimized cilnidipine orodispersible tablets to explore its taste evaluation, bioavailability, and therapeutic efficacy in patients with hypertension.

5 Conclusions

BCS class II drug, cilnidipine, was formulated into an orodispersible tablet by performing a solid dispersion technique to enhance the solubility of the drug and to improve patient compliance. Three formulations of solid dispersion (SD1, SD2, SD3) were prepared using PVP as a carrier by solvent evaporation method. Among the preparations, SD3 showed increased solubility in pH 6.8 citrophosphate buffer with SLS 0.2% up to 142-fold when compared with pure drug and other formulations. Hence, SD3 was selected as an optimized batch for the formulation of orodispersible tablets. The reduction in the crystallinity of the drug was confirmed by XRD and DSC studies. Orodispersible tablets was formulated using different super-disintegrants such as Crospovidone, croscarmellose, sodium starch glycolate in different ratios and combinations. Initially, based on the pre- and post-compression evaluations, drug content, disintegration time, and in vitro drug release studies results that the formulation F11 containing crospovidone and sodium starch glycolate in high concentration have shown least disintegration time of 26.6 s and in vitro drug release of 88.62% in 10 min and it was considered as the best formulation. Finally, F11 was compared with the conventional marketed tablet and almost 88.62% of the drug was released in 10 min for the former wherein the latter exhibited a release of 83% in 60 min. From the study, it has been concluded that the combined effect of super-disintegrants shows a best result than when used alone. The combination of solid dispersion technique and orodispersible tablet serves as an effective approach of improving dissolution which may influence the oral bioavailability of cilnidipine.

Abbreviations

SD: Solid dispersion; PVP: Polyvinyl pyrollidone; CP: Crospovidone; CS: Croscarmellose; SSG: Sodium starch glycolate; MCC: Microcrystalline cellulose; Mg stearate: Magnesium stearate; FT-IR: Fourier transform infrared; XRD: X-ray diffraction; DSC: Differential scanning calorimetry.

Acknowledgements

The authors would like to thank PSG College of Pharmacy and PSG Institute of Advanced Studies for providing all the required facilities for performing this work.

Author contributions

"MM" contributed to the concept, design, data collection and processing, analysis and interpretation of data, literature search, and writing. "VS" contributed to supervision, analysis and interpretation of data, and critical reviews. Both authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors do not report any competing interest in this work.

Received: 10 January 2022 Accepted: 1 June 2022
Published online: 20 June 2022

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