Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2018, 10(3):51-60

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Solubility Enhancement by Solid Dispersion and Effervescence Assisted Fusion Technique Using Cilnidipine as a Model Drug

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ABSTRACT

The Poor Solubility of Drugs is a major problem which limits the development of highly potent pharmaceutics. Solubility Enhancement is one of the important parameters which should be considered for those drugs having poor aqueous solubility. Drugs belonging to Biopharmaceutical Classification System (BCS) class II are characterized by low aqueous solubility and high physiological permeability. Solid Dispersion Technique (SDM) and Effervescence Assisted Solid Dispersion Techniques (EASDT) using Modified Fusion Method are the process to enhance the solubility of poorly water soluble drugs. In this work, BCS class-II drugs Cilnidipine is used as a model drugs, having poor solubility but high permeability is individually incorporated with Mannitol, Citric acid, and Sodium bicarbonate (Hydrophilic Carriers used as Excipients) in different ratio respectively. SDMs of Cilnidipine were prepared by melting (Fusion) method using Mannitol. Scanning electron micrographs of EASDs showed better uniform distribution of drug particles in the carrier matrix. The present technique is better suitable for drugs having a low melting point or melt without charring.

Keywords: EASDs; Solid dispersion; Cilnidipine; Solubility enhancements

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INTRODUCTION

High blood pressure affects more than 1 billion people worldwide and among these more than 72 million people are from United States. Hypertension is also a public health problem in developing countries like India. The major goals for enhancing solubility in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen as well as to increase the aqueous solubility of poorly water soluble drugs. The present works deals with the preparation and characterization of Cilnidipine complex using solid dispersion technique (SDT) and effervescence assisted solid dispersion technique (EASDT) by using modified fusion method for solubility enhancement [1-4]. This technique is useful for those drugs which are poorly soluble in water. Cilnidipine (2, 6-Dimethyl-4-(3-nitro-phenyl)-pyridine-3, 5-dicarboxylic acid 3-(2-methoxy-ethyl) ester 5-(3-phenyl-allyl) ester), (Figure 1) belongs to the Anti-hypertensive Drugs. It is a unique di-hydro pyridine derivative L-type calcium channel blocker with an inhibitory action on the sympathetic N-type calcium channels [5,6].

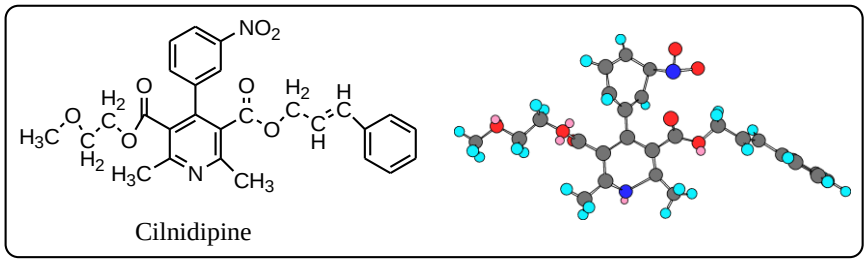

Figure 1: 2D and 3D structure of cilnidipine

MATERIALS AND METHODS

Materials

Cilnidipine was purchase from Pure Chem. Pvt. Ltd. Gujarat). Instrument were used for characterization are Electronic balance, FTIR (Shimadzu Corporation), UV-Vis spectrophotometer (Thermo scientific), Scanning Electron Microscopy (JEOI Model JSM-6390 LV), DSC (Mettler Toledo DSC 822e), PXRD (Bruker Axs D8 Advance) and Stability Chamber (Medical Equipment, India) etc. The best quality of entire chemicals were used like Acetonitrile, Methanol, Ortho phosphoric and Hydrochloric Acid (LR grade, Merck), Mannitol (Central drug house, New Delhi).

Methods

Preformulation studies of Cilnidipine (CPN) pure drug was carried out using Drug identification test, Determination of Melting point (capillary method), Solubility of CPN studies in distilled water, Acetonitrile, methanol, Ethanol, 0.1 N HCl and 0.1 N NaOH. In UV characterization, $\lambda_{max.}$ of CPN was determined using Methanol: Water (30:70) scanned between 200-400 nm and Calibration curve was prepared. Micromeretics properties of pure CPN drug was studies by determining of bulk density, Tapped Density, Car's Index, Angle of Repose and Hauser's Ratio. The size distributions along the volume mean diameters of the suspending particles were measured using dynamic scattering particle size analyzer [7,8]. Differential Scanning Calorimetry (DSC) analysis was performed using Samples (3-5 mg) were crimped in non-hermetic aluminium pans with lids and scanned from 50 to 300°C at a heating rate of 10ºC/min under a continuously purged dry nitrogen atmosphere (flow rate 20 mL/min). The instrument was equipped with a refrigerated cooling system**.** The FT-IR spectra of CPN pure drug were obtained over the range 400-4000 cm^{-1} in dry KBr (50 mg) and samples (1-2 mg). The X-ray diffraction (XRD) pattern of both drug were recorded under following conditions: voltage 35 kV, 20 mA, angular range 5, divergence slit 10, and receiving slit 0.15 mm. Surface morphology of the pure CPN was determined using a scanning electron microscope (SEM), operated at low accelerating voltage of about 15KV with load current about 80 mA [9-11].

Preparation of Cilnidipine Complex using Solid Dispersion Method (SDM) [12-15]

The Complex of Cilnidipine Solid dispersions were prepared using melting (fusion) method. Mannitol was melted in china dish on a heating mantle, and drug powder of Cilnidipine (10mg) was added to the molten mannitol on the basis of stoichiometric ratio (Table 1). The molten mixture of drug and carrier was continuously stirred to increase uniform distribution of components. This melted uniform mixture was quickly solidified at low temperature under cold condition (freezer) (Figure 2). Cooled solid dispersions were crushed and ground gently using a mortar and pestle. The complex of solid dispersion of drug was stored in desiccators in a Petridis.

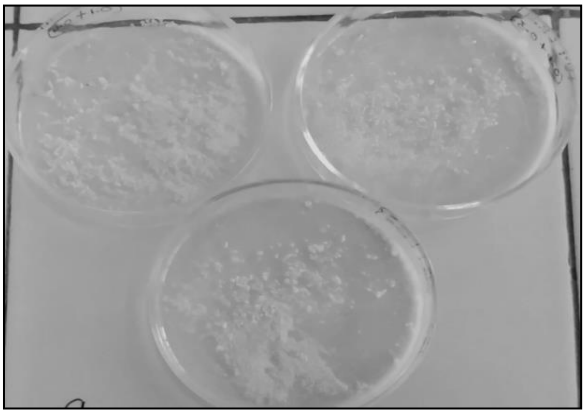

Figure 2: Cilnidipine complex using SDM

Table 1: Formula design of the cilnidipine complex using SDM

S. No.	Batch code	Drug (Cilnidipine) in mg	Excipient (mannitol) in mg
1	B1	10	30
2	B2	10	40
3	B3	10	50

Preparation of CPN Complex using EASD Method [16-19]

Carrier (mannitol) was melted in a china dish (at 175–180°C), and organic acid (citric acid) was added to the molten mannitol. This mixture of mannitol and organic acid was melted and uniformly mixed by continuous stirring and added the drug powder of CPN with continuous stirring. Sodium bicarbonate (carbonic base) was used as carrier in which ratio of carbonic base and organic acid added according to their molar reactivity (Table 2). After addition of sodium bicarbonate, the effervescence (micro-bubbles) was generated due to acid–base reaction and the molten mixture turns into white froth. This frothy molten mixture was continuously stirred until the effervescence slowed down (about to seize). The froths were cooled down and allowed to solidify at low temperature (freezer). This cooled solid dispersion was crushed and ground gently using a mortar and pestle (Figure 3). The Complex of EASD of drug was stored in desiccators in a Petridis.

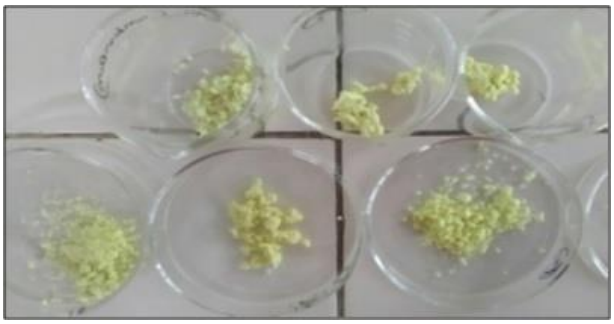

Figure 3: CPN complex EASD method

Table 2: Formula design of the CPN complex using EASD method

S. No.	Batch code	Drug (CPN) in mg	Excipient (in mg) Mannitol	Citric acid	Sod. Bi Carbonate
1	B1	10	30	10	30
2	B2	10	40	125	375
3	B3	10	50	150	450
4	B4	10	50	150	400
5	B5	10	40	100	250
6	B6	10	40	200	250

Characterization / Evaluation of Cilnidipine Complex [20-22]

Micromeretics properties prepared complex were studies by determining of bulk density, Tapped Density, Car's Index, Angle of Repose and Hauser's Ratio. The percentage yield was determined using following formula-

$$Percentage\ yield = \frac{Practical\ yield}{Theoretical\ yield} \times 100$$

The FT-IR spectra of prepared CPN complex were obtained over the range 400- 4000 cm^{-1} in dry KBr (50 mg) and samples (1-2 mg). DSC analysis was performed using Samples (3-5 mg) by crimped in non-hermetic aluminium pans with lids and scanned from 50 to 300ºC at a heating rate of 10ºC/min under a continuously purged dry nitrogen atmosphere (flow rate 20 mL/min). The instrument was equipped with a refrigerated cooling system**.** The XRD pattern of both drug complex were recorded under the conditions: voltage 35 kV, 20 mA, angular range 5, divergence slit 10, and receiving slit 0.15 mm. Surface morphology was determined using a scanning electron microscope (SEM), operated at low accelerating voltage of about 15 KV with load current about 80 mA.

The solubility studies of CPN and their prepared complex were carried out in water or Menthol/water (70:30) solution and analyzed using a UV spectrophotometer and compare. The pH values of solubility media (water), mannitol solution (30 mg/ml), and solutions of EASDs (30 mg/ml) of individual drugs were measured at 22°C using a pH meter (Seven Easy pH; Mettler Toledo- AG, Switzerland).

Stability Studies of CPN Complex

Stability study of optimized formulation batch of prepared complex were stored at 4℃ ± 2℃ and 75% ± 5% RH for 3 months to access their stability were compliance with WHO guidelines for stability testing. After 30, 60, 90 days sample were withdrawn and determined solubility efficiency, color, M.P and percentage assay [23].

RESULTS

CPN was found to be similar to the organoleptic properties standard reported in I. P. Melting point of CPN Pure drug was found 110-112ºC (reported 107-112ºC) IP-2014. Results of Solubility studies reported in Table 3. λ_{max} for CPN was found 241 nm (Figure 4). All Micrometric Property values were found to be in range, indicating good flow property of the API (Table 4). Results of particle size distribution reported in Table 5 and Figure 5.

Table 3: Solubility of CPN pure drug

S. No.	Cilnidipine Solvent	Pure Drug Inference
1	Distilled water	Insoluble
2	0.1 N HCl	Slightly soluble
3	0.1 N NaOH	Poorly soluble
4	Methanol	Freely soluble
5	Ethanol	Freely soluble

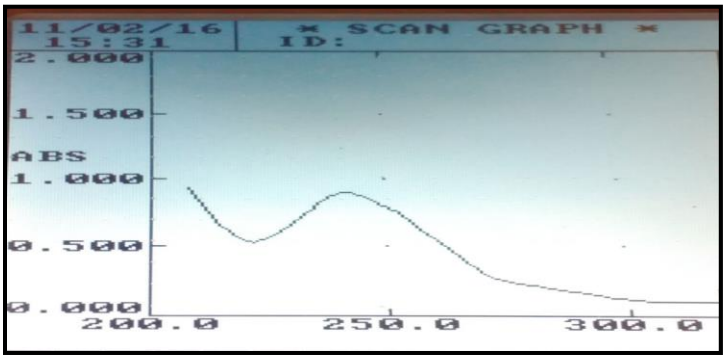

Figure 4: Absorbance spectra of CPN

Table 4: Values of micrometric property for CPN pure

S. No	Micromeretics parameters	CPN Pure Drug	
		Reported values	Observed values
1	Angle of repose(◦)	31º -35º	32º ± 0.34
2	Bulk density (gm/cm^3)	0.41 - 0.48	0.45 ± 0.02
3	Tapped Density (gm/cm^3)	0.51 - 0.59	0.53 ± 0.02
4	Hausner's Ratio	1.16 - 1.36	1.17 ± 0.18
5	Compressibility (%)	15 - 19	17 ± 0.52

Table 5: Particle size distribution of CPN

Frequency (µm)	0-10	Oct-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100
Count(no.)	10	20	75	305	225	185	160	110	35	15

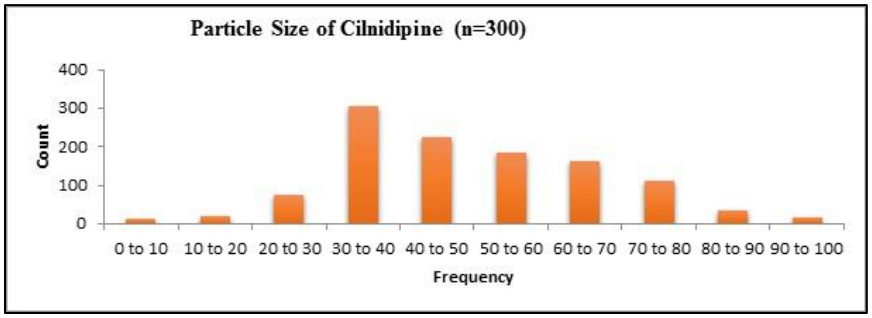

Figure 5: Particle size distribution of CPN (pure)

Results of Characterization/Evaluation for CPN Complex (Tables 6 and 7) (Figures 6-11)

Table 6: Micrometric properties of CPN complex

S. No	Code	SDM method				
		Bulk Density	Tapped Density	Carr's Index (%)	Hausner's Ratio	Angle of Repose (◦)
1	B1	0.44 ± 0.01	0.52 ± 0.02	16.76 ± 0.52	1.16 ± 0.18	32º ± 0.33
2	B2	0.43 ± 0.02	0.51 ± 0.01	15.77 ± 0.51	1.17 ± 0.17	31º ± 0.32
3	B3	0.45 ± 0.02	0.53 ± 0.02	17.76 ± 0.52	1.17 ± 0.18	33º ± 0.34
S. No	Code	EASD method				
1	B1	0.43 ± 0.01	0.52 ± 0.01	16.76 ± 0.51	1.16 ± 0.18	32º ± 0.34
2	B2	0.43 ± 0.02	0.52 ± 0.02	16.77 ± 0.52	1.17 ± 0.17	31º ± 0.32
3	B3	0.47 ± 0.02	0.55 ± 0.02	18.77 ± 0.52	1.18 ± 0.18	34º ± 0.34
4	B4	0.42 ± 0.01	0.51 ± 0.02	16.76 ± 0.52	1.16 ± 0.18	32º ± 0.33
5	B5	0.43 ± 0.02	0.51 ± 0.01	15.77 ± 0.52	1.16 ± 0.17	31º ± 0.32
6	B6	0.44 ± 0.01	0.52 ± 0.02	17.76 ± 0.51	1.17 ± 0.18	32º ± 0.33

Table 7: Percentage yield of CPN complex

S. NO.	Batch Code	SDM method		
		Theoretical Yield (mg)	Practical Yield (mg)	% Yield
1	B1	40	32.4	81%
2	B2	50	39.9	79.80%
3	B3	60	41	68.33%
S. NO.	Batch Code	EASD Methods		
1	B1	800	62.8	78.50%
2	B2	550	489	88.90%
3	B3	660	400	60.60%
4	B4	610	510	83.60%
5	B5	400	298	74.50%
6	B6	500	316	63.20%

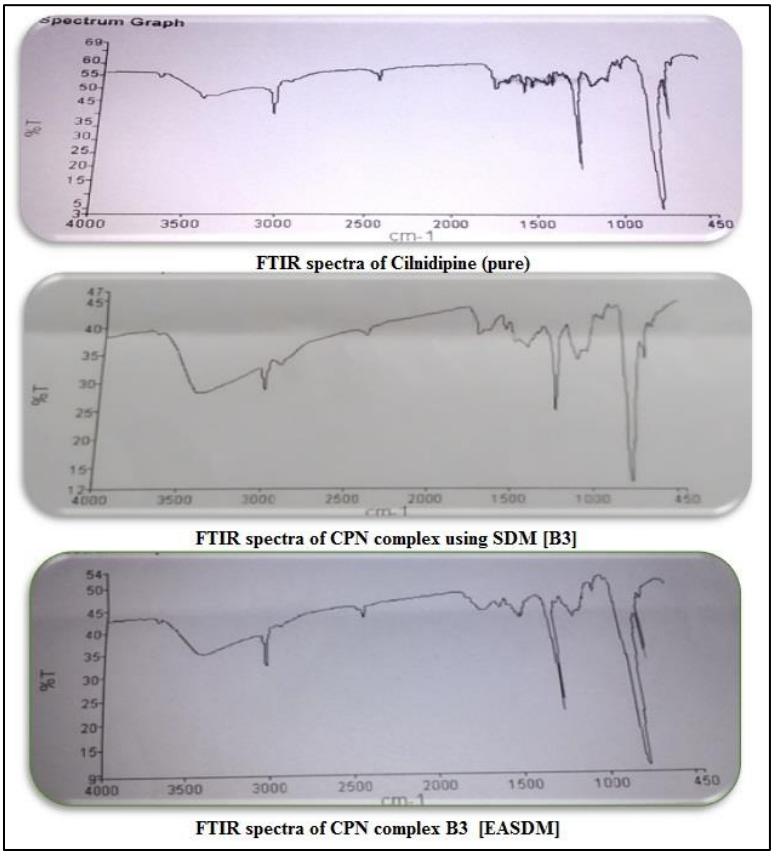

Figure 6: FTIR spectra of pure CPN and optimized prepared complex

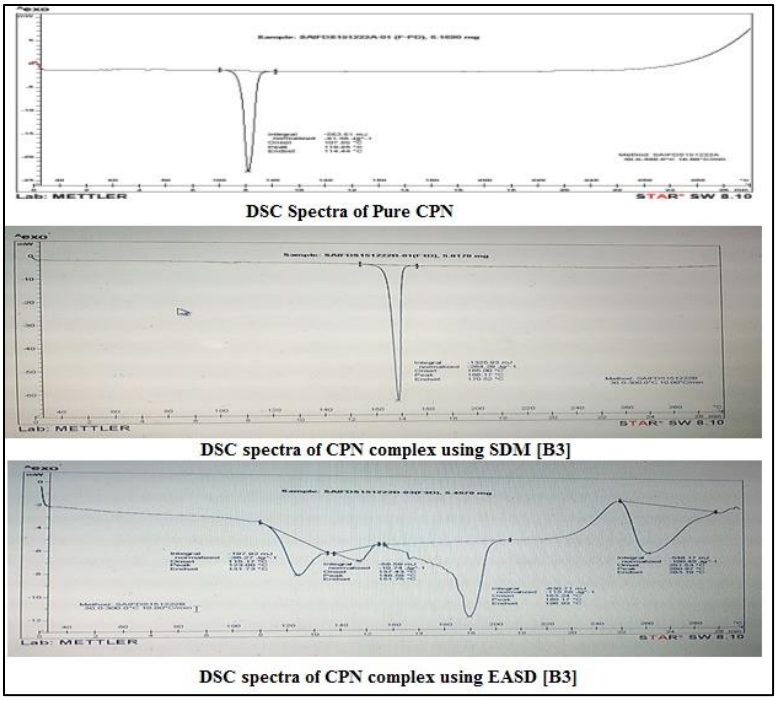

Figure 7: DSC spectra of CPN and optimized complex

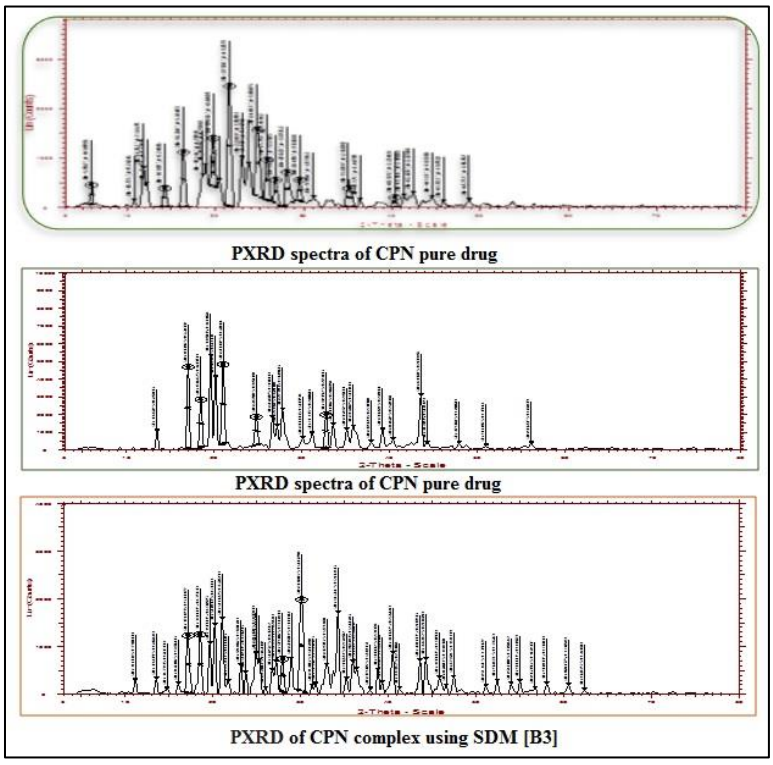

Figure 8: PXRD spectra of pure CPN and optimized complex

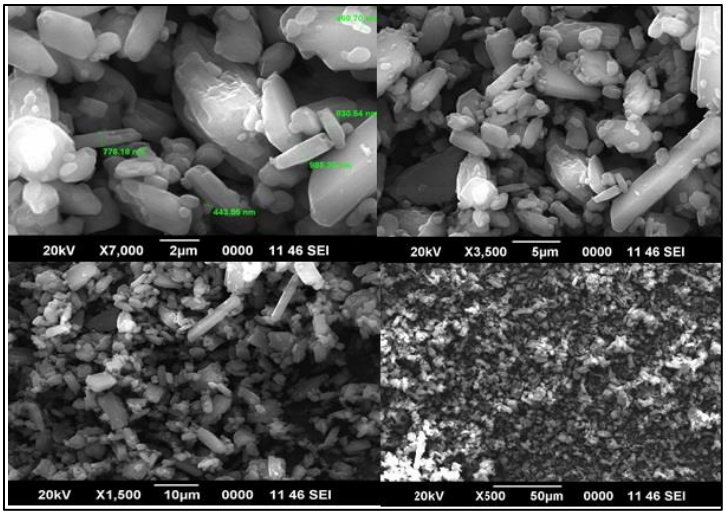

Figure 9: SEM structure of cilnidipine (pure)

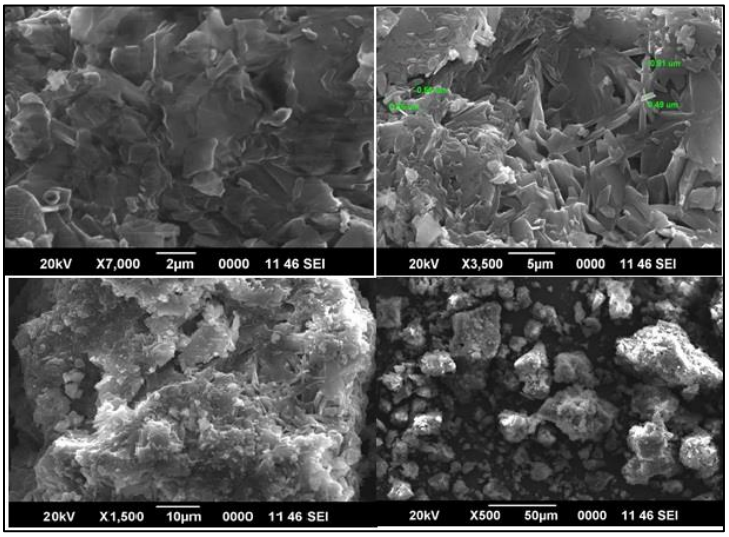

Figure 10: SEM of cilnidipine complex using SDM (B3)

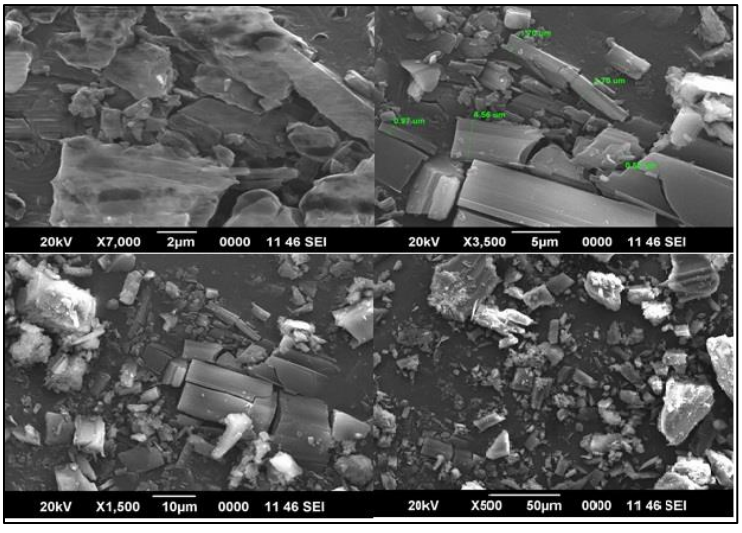

Figure 11: SEM of cilnidipine complex using EASD (B3)

Solubility of Cilnidipine complex using SDM and EASD method indicated that solubility of both SDM (B3) and EASD (B3) was increased as compare to the pure drug. Results are reported in Table 8 and Figure 12. The percent (%) drug content of all batches of SDMs and EASDs of CPN complex was found within range between 97%-99.12% which was within the limits of IP specifications (Table 8 and Figure 13). Results of stability studies and assay reported in Table 9.

Table 8: Water solubility and %drug content of CPN complex

Batch code	Complex CPN (SDM)	% Drug Content ± SD (n=3)
Pure Drug (≤ 2 mg/ml)	-----	----
B1	1.97	97 ± 0.46
B2	1.96	98 ± 0.70
B3	2.6	99 ± 0.48
EASD complex		
B1	1.96	97 ± 0.48
B2	1.96	97 ± 0.46
B3	2.9	99 ± 0.39
B4	1.97	97 ± 0.48
B5	1.95	98 ± 0.58
B6	1.96	97 ± 0.46

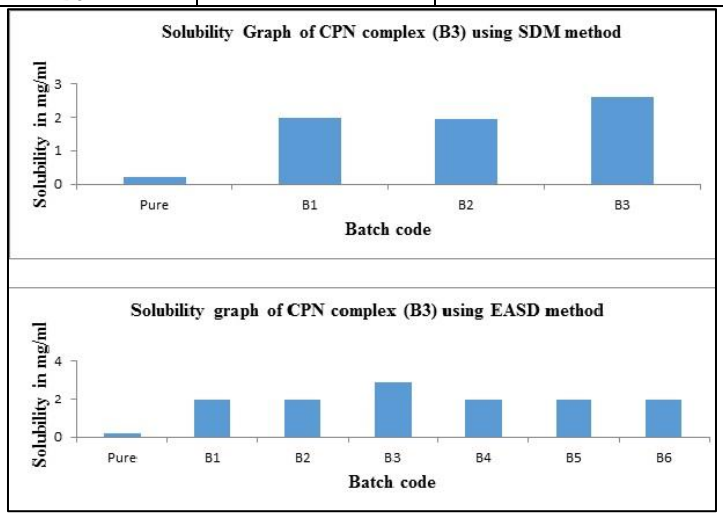

Figure 12: Solubility of CPN complex SDM (B3) and EASD (B3) methods

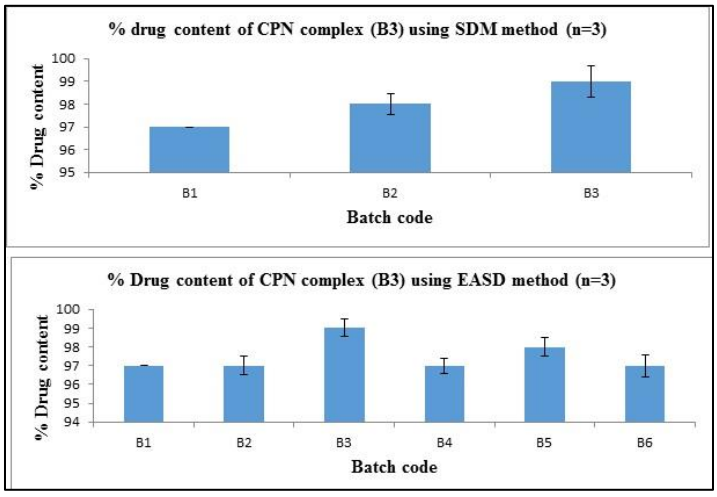

Figure 13: Results of stability studies

Table 9: Stability study and %assay of CPN complex SDM (B3) and EASDM (B3)

Time	Solubility Efficiency of B3 (SDM)	Color	M. P.	% Assay
Initial	2.6	Light yellowish	166-168ºC	98
After 3 month Storage				
1months	2.6	Light yellowish	166-168ºC	97
2months	2.5	Light yellowish	163-165ºC	97
3months	2.4	Light yellowish	162-164ºC	96
Time	**B3 (EASDM)**	**Color**	**Melting Point**	**% Assay**
Initial	2.9	Light Yellowish	189-191ºC	99
After 3 Month Storage				
1months	2.9	Light yellowish	189-191ºC	98
2months	2.8	Light yellowish	186-188ºC	97
3months	2.7	Light yellowish	183-185ºC	97

DISCUSSION

Micrometric properties of pure drugs as well as for SDMs and EASDs complex indicate god flow properties. The result shows that the melting point of CPN complex (SDM and EASD) is greater than CPN pure drug; whereas the EASDs show good melting peaks as compare to SDMs peaks. These facts imply that complex of SDMs and EASDs of CPN are crystalline in nature. XRD analysis of CPN complex show several weak peaks compared to pure CPN, it is cleared that particle size will decreased. SEM image indicate good shape and size. Solubility of CPN complex was increased as compare to the pure drug but SDMs [B3] and EASDM [B3] show good solubility but after comparing it was found that the solubility of EASDs has best solubility than SDMs. Stability studies indicating that optimized formulation is stable.

CONCLUSION

Effervescence assisted solid dispersion technique (EASD) provides an increase in the solubility of poorly water soluble drugs Cilnidipine. This technique can also be exploited for other poorly soluble drugs to enhance their solubility.

ACKNOWLEDGEMENT

The authors very sincere thankful to Shambhunath Institute of Pharmacy, Allahabad for providing the facilities of this research work.

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