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Formulation and evaluation of solid dispersion method based fast dissolving tablet of Cilnidipine

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Abstract

Background: The objective of this work was to enhance the solubility and dissolution rate for rapid onset of anti-hypertensive action of cilnidipine.

Method: To enhance the solubility of cilnidipine solvent evaporation method was used. In solvent evaporation method polymer like HPMC, PVP K30, PEG 4000 and PEG 6000(for binary solid dispersion) and poloxamer 188(for ternary solid dispersion) were used in the different drug polymer ratio.

Conclusion: Among them cilnidipine: HPMC: poloxamer 188 shows better solubility and also different physical characterization test like DSC and XRD. After selection of best ternary solid dispersion fast dissolving tablets of cilnidipine were prepared using direct compration method via using different super disintegrant.

Keywords: Cilnidipine; Solid dispersion; Fast dissolving tablet; Poloxamer; Ternary complex

1. Introduction

Solubility is the concentration of a solute in a saturating solution at a certain temperature when it is at equilibrium. Solid dispersion is one of the methods used to improve the dissolution of poorly soluble medications with a low absorption rate. "A dispersion involves the production of eutectic mixes of pharmaceuticals with water soluble carriers by melting of their physical mixtures," Chiou and Liegeman define solid dispersion.

Solid dispersion refers to the solid state dispersion of one or more active ingredients in an inert carrier or matrix, which can be achieved through melting (fusion), solvent, or the melting solvent method. The poorly water soluble medicine with low dissolution rate after administration, notably for class II compounds according to the biopharmaceutics classification system, indicating limited bioavailability (BCS). The medicines in BCS class II have a low solubility but a high penetration rate.

Cilnidipine acts on the L-type calcium channels of blood vessels by blocking the incoming calcium and suppressing the contraction of blood vessels, thereby reducing blood pressure. Cilnidipine also works on the N-type calcium channel located at the end of the sympathetic nerve, inhibiting the emission of epinephrine and suppressing the increase in stress blood pressure.

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2. Material and methods

Cilnidipine obtained as a gratis sample from Pure Chem. Pvt. Ltd; All other excipients were used of analytical grade.

2.1. Method of solid dispersion

Solid dispersion of cilnidipine was prepared by Solvent evaporation method.The drug and carrier (HPMC, PVP K30, PEG 4000 and PEG 6000) were dissolved in methanol in separate beakers. Both solutions were mixed in a beaker and stirred until the solvent evaporated completely. The resulting solid mass was passed through sieve no. 85 #. The resulting mass was transferred to desiccators and stored until further use.

2.2. Method of fast dissolving tablet (Direct compression)

All the ingredients were accurately weighed and pass through different mass sieves accordingly except magnesium stearate and talc, all other ingredients were blended in mortar uniformly.Later, magnesium stearate and talc was added, and the tablets were compressed using tablet punching machine.

Table 1 Composition of Binary (SB) and Ternary (ST) solid dispersion mixture

Formulation code	Ingredients	Ratio	Formulation code	Ingredients	Ratio
SB1	Cilnidipine + HPMC	1:1	ST1	Cilnidipine + HPMC + Poloxamer 188	1:5:1
SB2	Cilnidipine + HPMC	1:3	ST2	Cilnidipine + HPMC + Poloxamer 188	1:5:2
SB3	Cilnidipine + HPMC	1:4	ST3	Cilnidipine + HPMC + Poloxamer 188	1:5:3
SB4	Cilnidipine + PVP K30	1:1	ST4	Cilnidipine + PVP K30 + Poloxamer 188	1:5:1
SB5	Cilnidipine + PVP K30	1:3	ST5	Cilnidipine + PVPK30 + Poloxamer 188	1:5:2
SB6	Cilnidipine + PVP K30	!:5	ST6	Cilnidipine + PVPK30 + Poloxamer 188	1:5:3
SB7	Cilnidipine + PEG 4000	1:1	ST7	Cilnidipine + PEG4000 + Poloxamer 188	1:5:1
SB8	Cilnidipine + PEG 4000	1:3	ST8	Cilnidipine + PEG4000 + Poloxamer 188	1:5:2
SB9	Cilnidipine + PEG4000	1:5	ST9	Cilnidipine + PEG4000 + Poloxamer 188	1:5:3
SB10	Cilnidipine + PEG6000	1:1	ST10	Cilnidipine + PEG6000 + Poloxamer 188	1:5:1
SB11	Cilnidipine + PEG 6000	1:3	ST11	Cilnidipine + PEG6000 + Poloxamer 188	1:5:2
SB12	Cilnidipine + PEG 6000	1:5	ST12	Cilnidipine + PEG6000 + Poloxamer 188	1:5:3

Table 2 Formulation table of fast dissolving tablet

Ingredients (mg)	A1	A2	A3	A4	A5	A6	A7	A8	A9
Ternary solid dispersion of cilnidipine	e.q. to 10mg of cilnidipine	e.q. to 10mg of cilnidipine	e.q. to 10mg of cilnidipine	e.q. to 10mg of cilnidipine	e.q. to 10mg of cilnidipine	e.q. to 10mg of cilnidipine	e.q. to 10mg of cilnidipine	e.q. to 10mg of cilnidipine	e.q. to 10mg of cilnidipine
SSG	7.5	7.5	7.5	10	10	10	12.5	12.5	12.5
Crossprovidone	7.5	10	12.5	7.5	10	12.5	7.5	10	12.5
MCC	130	127.5	125	130	127.5	125	130	127.5	125
Sodium saccharine	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
Total weight	250	250	250	250	250	250	250	250	250

3. Result and discussion

Table 3 Solubility of binary and ternary solid dispersion

Formulation code	Solubility (mg/ml)	Formulation code	Solubility (mg/ml)
SB1	0.0246 ± 0.0022	ST1	0.3431 ± 0.0020
SB2	0.0372 ± 0.0021	ST2	0.4812 ± 0.0018
SB3	0.0495 ± 0.0020	ST3	0.5648 ± 0.0026
SB4	0.0186 ± 0.0018	ST4	0.1983 ± 0.0019
SB5	0.0261 ± 0.0026	ST5	0.2806 ± 0.0015
SB6	0.0343 ± 0.0019	ST6	0.3471 ± 0.0017
SB7	0.0218 ± 0.0015	ST7	0.2532 ± 0.0020
SB8	0.0326 ± 0.0023	ST8	0.3826 ± 0.0021
SB9	0.0357 ± 0.0016	ST9	0.4713 ± 0.0018
SB10	0.0194 ± 0.0017	ST10	0.2384 ± 0.0017
SB11	0.0286 ± 0.0015	ST11	0.3812 ± 0.0021
SB12	0.0398 ± 0.0022	ST12	0.4816 ± 0.0016

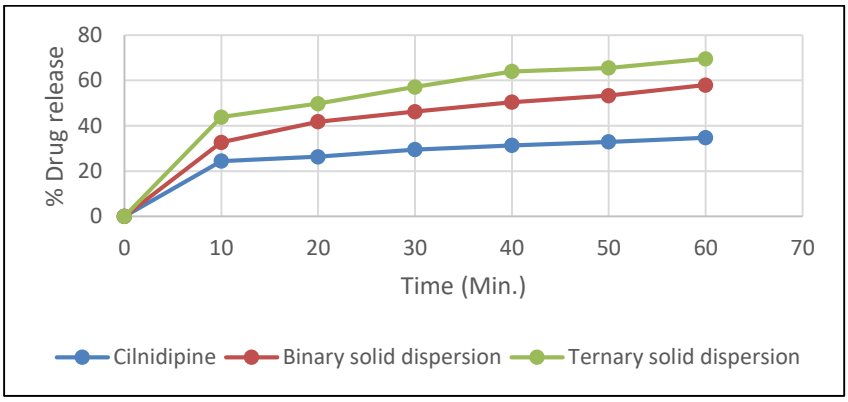

Figure 1 Comparison of *in-vitro* drug release of Drug, Binary and Ternary solid dispersion

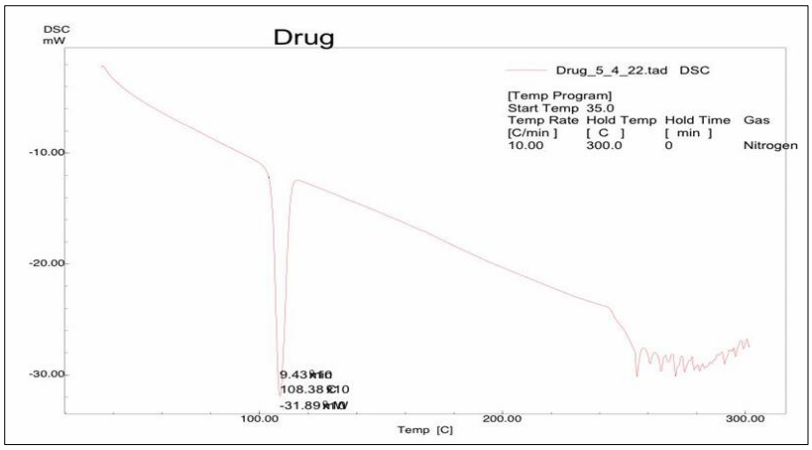

Figure 2 DSC spectra of pure cilnidipine

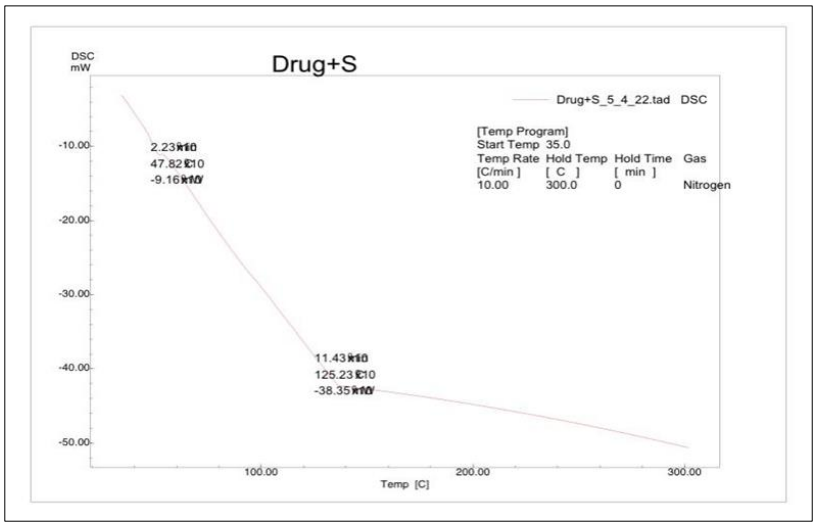

Figure 3 DSC spectra of ternary solid dispersion (ST3)

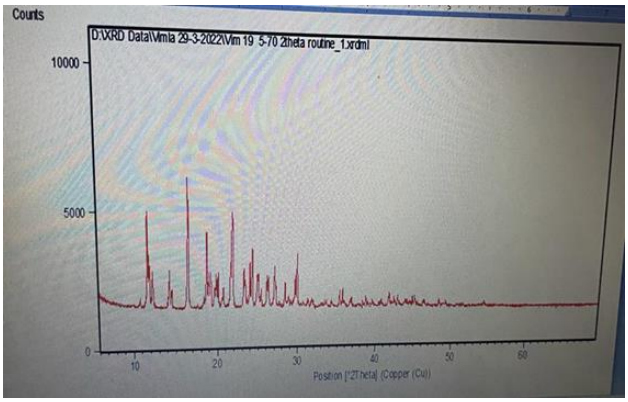

Figure 4 XRD image of pure cilnidipine

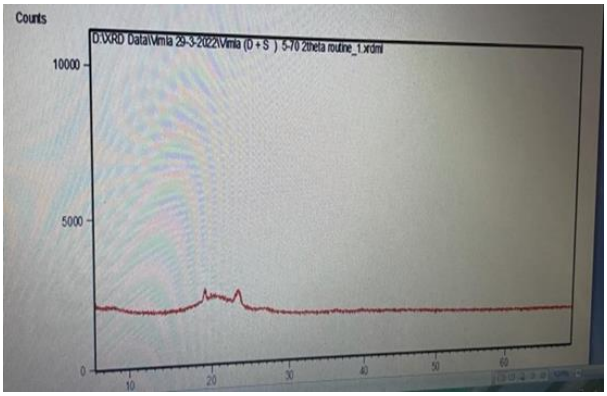

Figure 5 XRD image of ternary solid dispersion (ST3)

Table 4 Pre formulation study of fast dissolving tablet (SD± n=3)

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio	Angle of repose (Θ)
A1	0.482 ± 0.017	0.578 ± 0.011	16.60 ± 0.41	1.19 ± 0.14	18.54 ± 0.12
A2	0.457 ± 0.038	0.534 ± 0.042	14.41 ± 0.22	1.16 ± 0.12	16.14 ± 0.17
A3	0.472 ± 0.013	0.571 ±0.026	17.33 ± 0.61	1.20 ± 0.11	17.21 ± 0.19
A4	0.428 ± 0.048	0.529 ± 0.020	19.09 ± 0.71	1.23 ± 0.17	18.01 ± 0.17
A5	0.445 ± 0.056	0.547 ± 0.016	18.64 ± 0.42	1.22 ± 0.18	19.20 ± 0.14
A6	0.461± 0.070	0.572 ± 0.034	19.40 ± 0.21	1.24 ± 0.21	17.22 ± 0.19
A7	0.457 ± 0.082	0.567 ±0.048	18.53 ± 0.31	1.24 ± 0.13	17.28 ± 0.18
A8	0.424 ± 0.045	0.521 ± 0.053	18.61 ± 0.42	1.22 ± 0.18	16.18 ± 0.16
A9	0.457 ± 0.034	0.572 ± 0.064	20.10 ± 0.11	1.25 ± 0.11	18.21 ± 0.10

Table 5 Post formulation study of fast dissolving tablet (SD ± n=3)

Formulation code	Average weight (mg)	% Friability	Drug content	Hardness	Disintegration time (sec.)	Wetting time (sec.)
A1	245.67 ± 3.21	0.65	97.67±1.29	3.46 ± 0.54	84.15 ± 0.42	59.8 ± 0.5
A2	252.12 ± 2.53	0.44	99.46±0.57	3.64 ± 0.47	86.29 ± 0.38	48.6 ± 0.3
A3	248.34 ± 2.65	0.63	96.12±1.75	3.98 ± 0.32	72.98 ± 0.76	54.1 ± 0.4
A4	253.87 ± 3.75	0.53	98.53±1.32	3.51 ± 0.12	87.36 ± 0.65	59.7 ± 0.6
A5	256.25 ± 2.48	0.72	97.59±2.41	3.12 ± 0.31	88.87 ± 0.54	50.4 ± 0.3
A6	247.38 ± 3.01	0.54	98.20±1.81	3.47 ± 0.52	76.32 ± 0.32	57.6 ± 0.4
A7	253.76 ± 3.26	0.58	97.43±1.41	3.30 ± 0.27	78.28 ± 0.48	56.7 ± 0.4
A8	251.15 ± 1.98	0.33	99.01±0.97	3.75 ± 0.15	69.04 ± 0.18	42.3 ± 0.2
A9	246.42 ± 2.97	0.62	97.24±1.96	2.86 ± 0.43	82.76 ± 0.62	52.5 ± 0.5

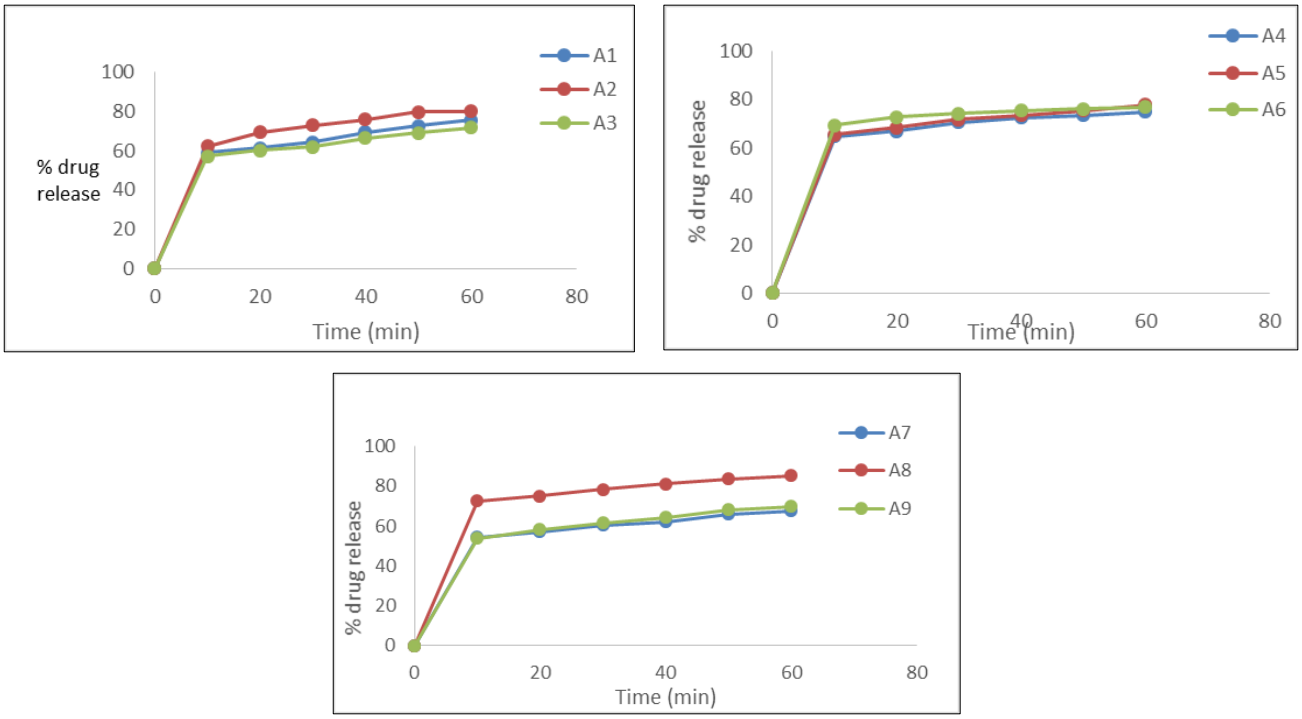

Figure 6 *In-vitro* drug release of fast dissolving tablet of cilnidipine

4. Conclusion

The binary dispersions of cilnidipine with the HPMC and its ternary dispersions with HPMC and poloxamer 188 were successfully prepared by the solvent evaporation method. The study demonstrated that the ternary dispersions system of the cilnidipine given higher dissolution rates as compared to pure drug and also their binary dispersion. Due to the presence of surfactant in the ternary system, there was more amorphizing effect as compared to binary solid dispersion as confirmed by the DSC and XRD study. The intermolecular interaction between drug and carriers leading to better dispersion of drug in the polymer matrix, reduction in size of drug particles, increase in the amorphous nature, increase in wettability and decrease in surface tension resulted in enhanced dissolution of the drug from the ternary dispersion

systems. Fast dissolving tablet containing superdisintegrant crosprovidone (4%) and SSG (3%) given a better dissolution and disintegration time.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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