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Original Article

Formulation and evaluation of orodispersible tablet of clinidipine by sublimation method

Gaurav Agarwal*, Shilpi Agarwal, Renu Kamboj, P.K. Karar

Faculty of Pharmacy, RP Educational Trust Group of Institutions, Karnal (Haryana) India-132001

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ABSTRACT

The aim of the present investigation was to develop oral disintegrating tablets of Cilnidipine. Oral disintegrating tablets (ODTs) by sublimation method. Disintegration time, resistance to crushing of tablets, porosity, friability, disintegration time and dissolution profiles of ODTs were investigated. All tablet formulations disintegrated within one minute and fulfilled the three minute disintegration time required for ODTs as given in European Pharmacopoeia. No interaction or changes were found between active substance and excipients. As a result of the studies, ODT formulations developed in this study can be suggested as promising formulation which assist development and manufacturing of orodispersible tablet of Cilnidipine.

Key Words: Cilnidipine, Orodispersible tablet, Sublimation method

INTRODUCTION

Orodispersible tablet is an innovative tablet technology where the dosage form containing active pharmaceutical ingredients disintegrates rapidly usually in a matter of seconds without the need of water providing rapid onset of action to the patient. Innovators and inventor companies have given these tablets various names such as orally disintegrating tablets(ODT) mouth dissolving tablet (MDT) fast melting and fast dissolving tablets.[1,2] Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. In oral dosage forms tablets are most widely used dosage form because of its convenience in terms of ease of administration, accurate dosage, self-medication, better patient compliance and ease in manufacturing.[3,4]

Cilnidipine is a novel dihydropyridine calcium antagonist and its calcium antagonistc, activity is lasting longer than those of Nifedipine and Nicardipine. Cilnidipine has been used for the treatment of hypertension and hypertensive-associated vascular disorders. Its adult dose is about 40-80 mg once daily.[4] Cilnidipine has a very low solubility (BCS Class class-11 drug i.e low solubility high permeability) hence the first job is to enhance the solubility, dissolution rate & minimize the variability in absorption of Cilnidipine. The main objective to formulate these tablets for geriatric and pediatric patients who experience difficulty in swallowing tablet also for bed ridden. To provide the rapid onset of action there is need to develop rapidly disintegrating dosage form, particularly one that disintegrates and dissolves/disperses in saliva and can be administered without need of water. [5] In the present work, Cilnidipine was chosen as a model drug. Cilnidipine is a calcium channel blocker. It's acceptable taste makes that an ideal drug candidate for mouth dissolving tablet. An attempt was made in the present work to formulate and evaluate mouth dissolving tablets of Cilnidipine.

MATERIALS AND METHODS

Materials: Cilnidipine obtained as gift sample from CPA Pharma, Surat (Gujarat). Sodium starch glycolate, CCS, mannitol, aspartame, Mgsterate, Ammonium bicarbonate, Camphor, talc. LobaChemie Pvt.Ltd, Mumbai, S.D Fine Chemie, Mumbai.

Methods: Cilnidipine orodispersible tablets has been prepared by Sublimation method using various formulation additives in varying concentrations and detailed composition as shown in the table 1. The powder blend for direct compression and granules were then compressed

***Corresponding Author Address:** Dr. Gaurav Agarwal, Dean, Faculty of Pharmacy, RPIIT Technical and Medical Campus, Karnal, (Haryana) India; E.Mail: g.rpiit@yahoo.com, gbitsian@yahoo.com*

into tablets using 8 mm convex faced punches in a tablet punching machine. Tablets were then vacuum dried until they reached constant weight. During drying, the camphor and ammonium bicarbonate sublimated with the formulation of porous structure on the surface of the tablet.

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Cilnidipine	20	20	20	20	20	20	20	20
Ammonium Bicarbonate	30	-	-	30	-	55	-	55
SSG	-	30	30	30	-	-	-	30
Camphor	-	30	55	-	30	-	55	-
Crosscarmellose sodium	30	-	-	-	30	30	30	-
Maanitol	160	160	135	160	160	135	135	135
Aspartame	3	3	3	3	3	3	3	3
Mg.sterate	3	3	3	3	3	3	3	3
Talc	4	4	4	4	4	4	4	4
Total	250	250	250	250	250	250	250	250

Table 1: Composition of oral disintegrating tablets of Cilnidipine

PREPERATION OF STANDARD CURVE OF CILNIDIPINE

Standard curve of Cilnidipine was determined by plotting absorbance v/s concentration at 240 nm and it follows the Beer's law. The results were shown in table no.2. and figure number 1.

PREFORMULATIONSTUDIES [6,7]

Determination of melting point: Melting point of Cilnidipine was found in the range of 108°C, which complied with the standard, indicating purity of the drug sample.

Solubility: Cilnidipine is sparingly soluble in methanol and in ethanol on gentle heating, insoluble in water.

Compatibility Study: Compatibility studies were performed by doing DSC. The DSC of pure drug and physical mixture of drug and excipients were studied. The DSC of pure drug & other excipients were taken shown in figure 2and 3.

S.NO.	Concentration (µg/ml)	UV Absorbance at 240 nm
1	0	0.00
2	5	0.432
3	10	0.786
4	15	1.128
5	20	1.460
6	25	1.742

Table 2: Standard Calibration Curve

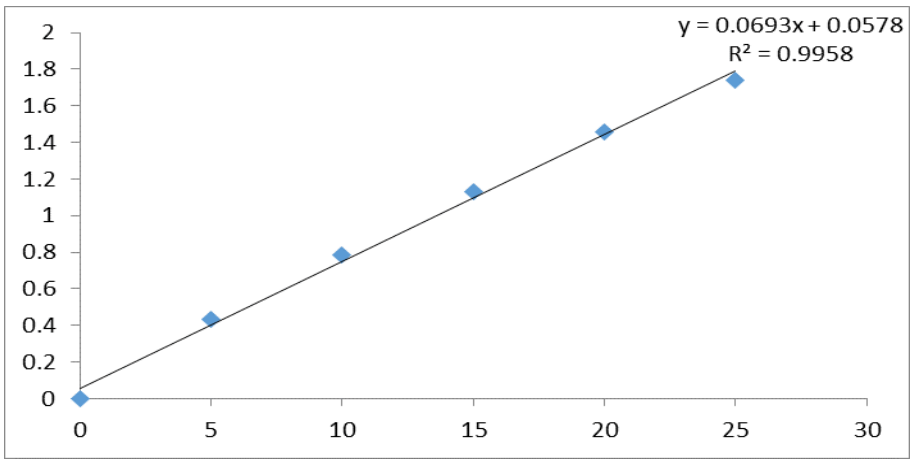

Fig1: Standard graph of Cilnidipine in methanol

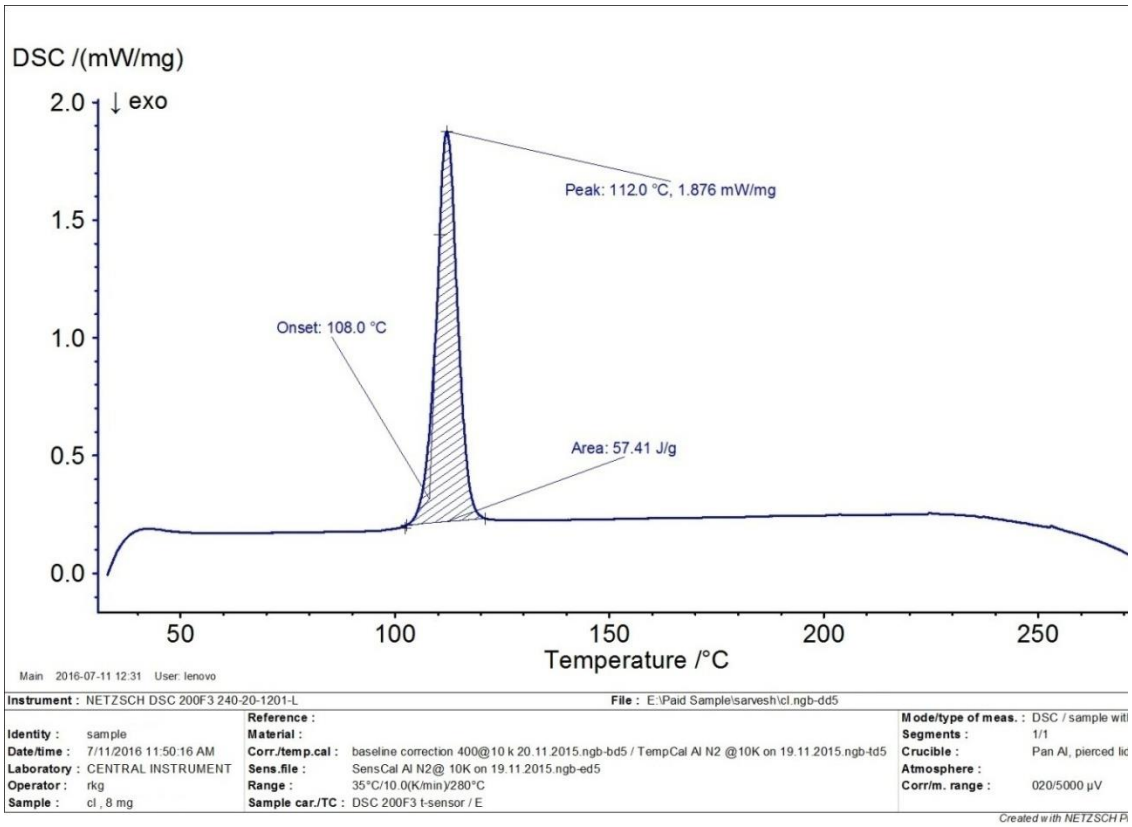

Fig2: DSC of Cilnidipine Pure drug

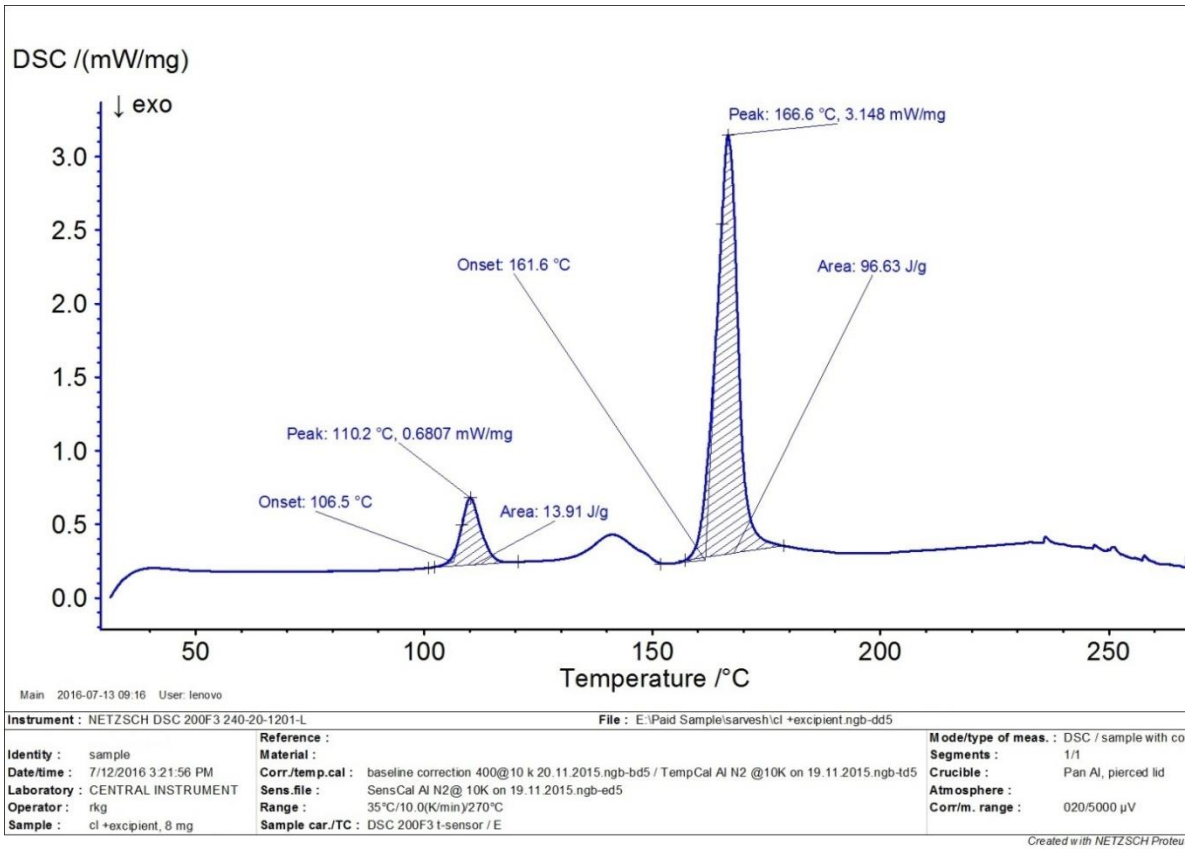

Fig3: DSC of Cilnidipine with Excipients

PRECOMPRESSION STUDIES

The granules for tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio.[8] Angle of repose was less than 31° and Carr's index values were less than 14 for the formulations of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.17 for all the batches indicating good flow properties depicted in table number 3.

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose (θ)
F1	0.65	0.73	10.95	1.12	28.9
F2	0.63	0.73	13.69	1.15	29.0
F3	0.60	0.69	13.0	1.15	28.9
F4	0.67	0.73	8.3	1.08	28.8
F5	0.63	0.70	10.0	1.11	29.9
F6	0.60	0.68	11.76	1.13	30.9
F7	0.61	0.69	11.59	1.13	30.9
F8	0.62	0.72	13.8	1.16	29.0

Table3: Pre compression studies Oral dispersible tablets of Cilnidipine

POSTCOMPRESSION STUDIES

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in the above table number 4. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between3.2% - 4.7%. The hardness of the tablets ranged from 3.1 to 3.3 kg/cm^2 and the friability values were less than 0.95% indicating that the tablets were compact and hard. Disintegration time ranged from 64 to 95Seconds and dispersion time was ranged from21-28 sec. All the formulations satisfied the content of the drug as they contained96.45% to 99.78%of Cilnidipine and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.

Formulation	Hardness Kg/cm^2	Friability (%)	Weight Variation	Content Uniformity	Disintegration Time (sec)	Dispersion Time(sec)
F1	3.3	0.95	3.3	96.45	95	28
F2	2.8	0.80	3.2	97.99	81	26
F3	3.0	0.89	3.7	99.67	71	23
F4	2.8	0.75	4.7	96.99	94	26
F5	3.2	0.86	4.5	98.79	80	25
F6	3.1	0.86	3.2	99.67	72	22
F7	3.1	0.75	3.9	99.78	64	21
F8	3.1	0.65	3.4	99.70	77	22

Table 4: Post compression Oral Disintegrating tablets of Cilnidipine

***In- Vitro* DRUG RELEASE STUDIES**

In-Vitro drug release studies were carried out using tablet dissolution test apparatus USPXXIII at 50 rpm depicted in table number 5and 6. The dissolution medium considered of 900 ml of Standard buffer 6.8 Phosphate buffer. Temperature maintained at 37±1. The sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. The samples withdrawn were filtered through Whitman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 240 nm. The dug release profile is shown in figure number 4 and 5.

Time(min)	F1	F2	F3	F4
0	0	0	0	0
2	32.07±0.66	44.17±0.93	44.99±0.95	31.12±1.42
4	46.01±0.99	48.15±0.72	56.03±1.72	43.01±1.32
6	49.01±1.47	55.5±1.04	60.11±1.19	49.12±1.59
8	51.09±1.76	60.11±0.94	71.14±1.31	55.83±1.39
10	65.19±1.44	71.72±0.81	76.91±0.61	64.39±1.15
12	72.10±1.43	76.91±1.32	92.01±1.12	70.89±1.39
14	79.51±1.31	90.99±1.35	98.19±1.32	79.84±1.94
16	92.57±1.59	100.72±0.69	90.21±0.91	94.66±0.94
18	99.54±1.71	90.73±1.38	82.19±1.37	98.12±1.59
20	89.71±0.83	82.49±1.99	73.11±1.27	90.17±1.11

Table 5: *In-Vitro* Release Data of Cilnidipine from F1-F4

Time(min)	F5	F6	F7	F8
0	0	0	0	0
2	44.17±1.39	42.99±0.19	58.51±0.91	51.19±1.61
4	49.34±1.99	50.19±1.52	58.99±0.59	59.16±1.90
6	57.19±1.39	58.17±1.16	70.53±1.52	65.13±1.49
8	59.13±1.94	70.02±1.99	78.49±0.79	73.41±1.08
10	74.04±1.39	77.36±1.19	83.83±1.11	81.11±1.5
12	76.94±1.47	95.16±0.99	91.99±0.33	93.25±0.51
14	89.71±0.74	99.99±0.90	100.39±0.39	100.00±1.97
16	99.12±0.73	92.19±0.48	93.40±1.1	93.88±1.92
18	92.39±0.74	84.65±1.59	83.14±1.50	85.40±1.39
20	81.17±1.99	74.94±1.35	70.19±1.19	72.19±1.5

Table 6*: In-Vitro* Release Data of Cilnidipine from F5-F8

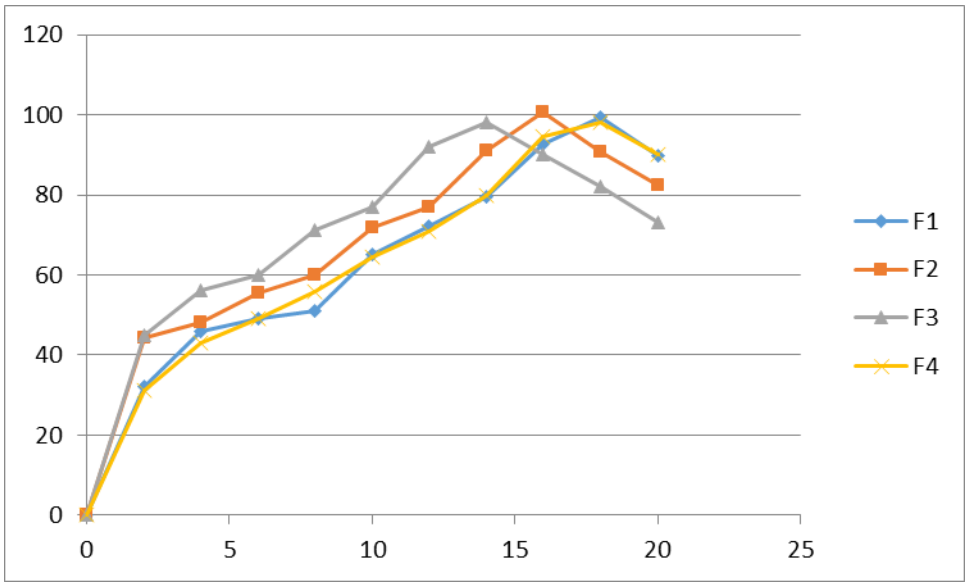

Figure 4: Release Profiles of Cilnidipine Formulations

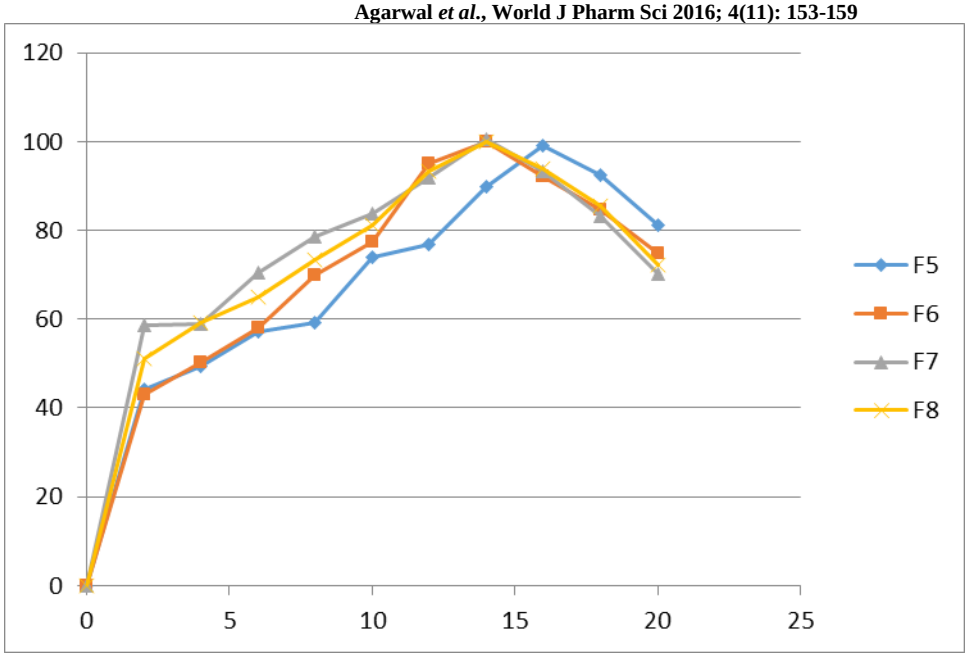

Figure 5: Release Profiles of Cilnidipine Formulations F5-F8

RESULTS AND DISCUSSIONS

Mouth dissolving tablets of Cilnidipine were prepared by Sublimation method employing Camphor and Ammonium bicarbonate as Sublimating agents in different concentration .A total of eight formulations were designed F1 (Ammonium bicarbonate 12% + CCS 12%), F2 (SSG 12% + Camphor12%), F3 (SSG 12% + Camphor 20%), F4 (Ammonium bicarbonate 12% + SSG 12%), F5 (Camphor 12% + CCS 12%), F6 (Ammonium bicarbonate 22% + CCS 12%), F7 (Camphor 22% + CCS 12%), F8 (Ammonium bicarbonate 22% + SSG12%).

The uniformity of mass of the tablets; the flow of the powder mixture was analyzed before compression to tablets. Low Hausner's ratio, compressibility index and angle of repose values indicated a fairly good flowability of powder mixture. Hardness and friability loss indicated that tablets had a good mechanical resistance. Drug content was found to be high in all the tablet formulations. The most important parameter that needs to be optimized in the development of fast dissolving tablets is the disintegration time of tablets, it was observed that the disintegration time of the tablets decrease with increasing level of camphor. However disintegration time also increased with increase in level of Ammonium bicarbonate in tablets .But formulations containing CCS and Camphor shows good results as compared to Camphor and SSG.

CONCLUSION

Melting point of Cilnidipine was found in the range of 108°C, which complies with the standard, indicating purity of the drug sample. Standard curve of cilnidipine was determined by plotting absorbance V/s concentration at 240nm and it follows the Beer's law. It was concluded that the formulation F7 containing 22% w/w Camphor and 12% CCS along with mannitol as a solubilizing agent was found to be promising and has shown the disintegration time of 64 second, drug content 99.78 %, wetting time 21 second and water absorption ratio of 59.21 % when compared to control formulations. The tablets exhibited good in-vitro dispersion, the release kinetics for the optimized formulation (F7) was determined. The formulation (F7) follows Higuchi model drug release kinetics with R^2 value of 0.9349.Thus the present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and better patient compliance.

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