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Formulation and Evaluation of Cilnidipine Solid Dispersions and Oral Controlled Release Formulations

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Abstract

The objective of the present study is to improve the solubility of Biopharmaceutical Classification System (BCS) Class-II drug, Cilnidipine by formulating them as solid dispersions and to make controlled released formulations. Solid dispersions of Cilnidipine were prepared by solvent evaporation technique using plasdone K-29/32. Various physical parameters were evaluated for the prepared solid dispersions. The *in vitro* drug release studies were performed for the solid dispersions using phosphate buffer pH 6.8. The solid dispersions which showed maximum drug release were selected for the preparation of oral controlled release formulations. Tablets were prepared using Cilnidipine solid dispersions and varying concentrations of polyethylene oxide (PEO) WSR 303 by direct compression technique. Pre and post-compression parameters were evaluated along with *in vitro* drug release studies. *In vitro* dissolution studies revealed that solid dispersion CP3 containing Cilnidipine and plasdone K-29/32 in 1:3 ratios showed faster drug release. Formulation CPP5 containing CP3 solid dispersion with 25% w/w of PEO WSR 303 showed prolonged drug release up to 12h. The solubility of Cilnidipine was enhanced using plasdone K-29/32 and the drug release was delayed using PEO WSR 303 as polymer.

Keywords: Cilnidipine, Solid dispersions, Plasdone K-29/32, Controlled release, PEO WSR 303.

Introduction

Solubility is an important factor for any drug to show its pharmacological effect in the body. Now a days, most of the drugs are facing the problem of aqueous solubility. In such cases, solubility enhancement could be helpful which could be beneficial for many patients (1). The water solubility of such drugs can be improved by various techniques. One of such most popular techniques is solid dispersions. They modify the drug properties and make them more soluble in water (2). Solid dispersions are the dosage forms with two major components; a hydrophobic drug and a hydrophilic carrier. They were made using various techniques like physical mixing, solvent evaporation and fusion (3). Solid dispersions dissolve drug in water by employing various mechanisms like making complexes, reducing the particle size, increasing wetting time (4). The drug concentration in body is maintained within the therapeutically effective range by conventional drug delivery systems only when taken multiple times in a day. This could be disadvantageous in case of geriatrics who ought to take many drugs in a day due to various disease conditions. Dosage forms which could retain in the stomach for prolonged and predictable period of time are advantageous in such cases (5). Prolonged gastric retention of drug also increases bioavailability, decreases wastage of drug and improves solubility for drugs that are less soluble in a high pH environment (6). This could be achieved by using certain polymers like polyethylene oxides (7). Poly ethylene oxides are hydrophilic in nature and are

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available in various grades. They help in prolonged drug release (8).

In current study, an attempt was made to enhance the solubility of BCS (Biopharmaceutical Classification System) class-II drug, Cilnidipine which is poorly soluble in water. It shows the anti-hypertensive effect by blocking L-type calcium channels on blood vessels. It also suppresses the contraction of blood vessels (9). The bioavailability of Cilnidipine is approximately 13%. It shows high binding to plasma proteins. It has an approximate elimination half-life of 2.5h. Based on pharmacokinetic parameters, Cilnidipine is selected as drug of choice for present study.

Materials and Methods

***Materials*:** Cilnidipine is a gift sample from M/s. NATCO Pharma Ltd. (Hyderabad, India). Plasdone K-29/32 and micro crystalline cellulose were gift samples from M/s. Pellets Pharma Ltd (Hyderabad, India). Poly ethylene oxide WSR 303 is a gift sample from M/s. Colorcon Asia Pvt Ltd., (Goa, India). Magnesium stearate and talc were procured form S.D Fine Chem. Ltd. (Mumbai, India).

***Preparation of Cilnidipine Solid Dispersions by Solvent Evaporation Method*:** Solid dispersions of Cilnidipine were prepared using plasdone K-29/32 as polymer in different ratios by solvent evaporation method (10). Measured quantities of Cilnidipine and Plasdone K-29/32 were placed in china dish. Few ml of methanol was added and heated at low temperature until both gets melted. The mixture was allowed to evaporate by continuous stirring. The solid mass obtained after the solvent evaporation was crushed and stored in desiccator for further study. The composition of various Cilnidipine solid dispersions. (Table 1).

***Evaluation of Physical Parameters of Cilnidipine Solid Dispersions*:** The prepared solid dispersions were evaluated for various physical parameters such as angle of repose, Carr's index, Hausner's ratio, particle size and drug content (11). The results were indicated in (Table 2).

Table 1. Composition of Cilnidipine Solid Dispersions Prepared by Solvent Evaporation Method

Formulation	Drug:Polymer (Cilnidipine*:Plasdone K-29/32)
CP1	1:1.0
CP2	1:2.0
CP3	1:3.0
CP4	1:4.0
CP5	1:5.0
*One part is equal to 10mg	

Table 2. Physical Parameters of Cilnidipine Solid Dispersions

Solid Dispersion	Angle of Repose (^{0})	Carr's Index (%)	Hausner's Ratio	Average Particle Size (µm)	Drug Content* (mg) (Mean ± S.D)
CD	33	23	1.28	42	09.64±0.98
CP1	24	19	1.22	188	10.04±0.47
CP2	22	16	1.18	172	09.99±0.63
CP3	20	12	1.15	156	10.08±0.31
CP4	22	14	1.17	164	09.95±1.03
CP5	23	15	1.18	169	10.11±0.32
*CD indicates Cilnidipine pure drug; n=3, S.D: standard deviation					

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Angle of Repose: The powder flow properties were determined to know the good or bad material flow. The powder was taken into a funnel and poured through it. Below this, a graph sheet was placed to form a heap like structure for which, the radius and height of the heap was measured. Based on these, the angle of repose was calculated by using the formula;

$\theta = \tan^{-1}(h/r)$

Carr's Index: A simple test was used to evaluate the flow ability of a powder by comparing the poured density and the tapped density of a powder and the rate at which it is packed down.

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Poured density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio: It is an indication of flow properties of the powder. Hausner's ratio can be calculated by using the formula;

$$\text{Hausner's Ratio} = \frac{\text{Tap density}}{\text{Bulk density}}$$

Particle Size: A set of sieves were taken, properly cleaned and are stacked in descending order of mesh size (increase in the sieve number). The solid dispersion was taken in the sieve number 18. The sieves are closed with lid and sieving was done for 5min. The material retained on individual sieves were collected and weighed.

Drug Content Uniformity: Solid dispersions of Cilnidipine equivalent to 10mg was weighed and transferred into a 100ml volumetric flask. To this, small quantity of methanol was added to dissolve. It was shaken occasionally for about 15min and the volume was made up to 100ml by methanol. The solution was filtered using Whattmann filter paper. The filtrate was subsequently diluted with 6.8pH phosphate buffer and the absorbance was measured at 240nm using 6.8pH phosphate buffer as blank.

In vitro Dissolution Studies of Cilnidipine Solid Dispersions: Dissolution studies for all solid dispersions were performed in a calibrated dissolution test apparatus (LABINDIA DS8000) equipped with paddles employing 900 ml of phosphate buffer pH 6.8 as dissolution medium. The paddles were operated at 50rpm and temperature was maintained at 37±1ºC throughout the experiment. The samples were withdrawn at 5, 10, 15, 20 and 30min and replaced with equal volume of same dissolution medium to maintain the sink conditions (12). The amount of the drug dissolved in the dispersions was estimated by double beam U.V spectrophotometer at 240nm. The dissolution profiles were indicated. (Figure 1).

Preparation of Cilnidipine Tablets: Cilnidipine tablets were prepared by direct compression technique using the solid dispersion which showed maximum drug release. The solid dispersion concentration was maintained constant, while the concentration of PEO WSR 303 was increased the range of 5% to 30% w/w of total tablet weight. The raw materials were individually weighed and transferred to mortar. Using pestle, the components were mixed well and the prepared granules were passed through sieve no. 40. The granules were taken into a plastic bag and lubricated with talc and magnesium stearate. Then they were compressed as tablets under identical conditions (13). The compositions of various tablet formulations. (Table 3).

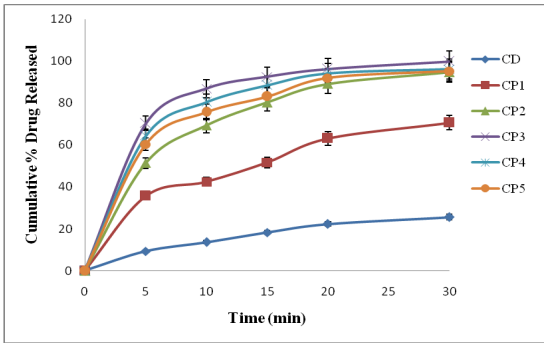

Fig 1. Drug Release Profiles of Cilnidipine Solid Dispersions

Mean ± S.D = Mean values ± Standard Deviation of three experiments

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***Evaluation of Pre-Compression Parameters*:** The prepared granules were evaluated for pre compression parameters such as angle of repose, Carr's index and Hausner's ratio (14). (Table 4).

***Evaluation of Post Compression Parameters*:** The compressed tablets were further evaluated for post compression parameters such as weight uniformity, hardness, friability, swelling index and drug content (15) (Table 5).

***Weight Uniformity*:** Twenty tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The weights of individual tablets were then compared with the average weight that was already calculated. The tablets meet the specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

***Hardness*:** The crushing strength/hardness which is the force required to break the tablet in the radial direction was measured using Monsanto hardness tester (Tab-machines, Mumbai). The tablet to be tested is held in fixed and moving jaw and reading of the indicator adjusted to zero. Then force to the edge of the tablet was gradually increased by moving the screw knob forward until the tablet breaks. The reading was noted from the scale which indicates the pressure required in kg/cm^2 break the tablet.

***Friability*:** Friability test was performed by using Roche friabilator (REMI Equipment, Mumbai). Ten tablets of a batch were weighted and placed in a friabilator chamber and it was allowed to rotate for 100 revolutions. During each revolution these tablets fall from a

Table 3. Composition of Cilnidipine Tablets

Ingredient (mg/tablet)	Formulations						
	CPP	CPP1	CPP2	CPP3	CPP4	CPP5	CPP6
Optimized Cilnidipine Solid Dispersion (CP3)	40	40	40	40	40	40	40
PEO WSR 303	----	12.50	25.0	37.50	50.0	62.50	75.0
MCC (PH 102)	205.0	192.50	180.0	167.50	155.0	142.50	130.0
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight	250	250	250	250	250	250	250

Table 4. Pre-Compression Parameters of Cilnidipine Granules

Formulation	Angle of Repose (^{0})	Carr's Index (%)	Hausner's Ratio
CPP	30	21	1.22
CPP1	26	19	1.18
CPP2	24	17	1.17
CPP3	23	16	1.15
CPP4	22	15	1.13
CPP5	21	12	1.12
CPP6	21	12	1.12

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Table 5. Post Compression Parameters of Cilnidipine Tablets

Formulation	Weight Uniformity (mg)	Hardness (kg/cm^2)	Friability (% loss)	Swelling Index (%)	Drug Content* (mg/tablet) (Mean ± S.D)
CPP	250±0.88	3.5±0.08	0.4	---	10.09±0.57
CPP1	249±0.94	3.3±0.05	0.3	90	09.96±0.82
CPP2	251±0.39	3.3±0.07	0.3	141	10.10±0.68
CPP3	250±1.01	3.2±0.10	0.3	185	10.01±1.03
CPP4	251±0.64	3.2±0.09	0.3	224	09.92±1.12
CPP5	250±0.82	3.3±0.04	0.3	262	10.05±0.93
CPP6	251±0.66	3.2±1.03	0.2	295	10.15±0.38
*n=6; S.D is standard deviation					

distance of six inches to undergo shock. After completion of 100 revolutions, tablets were again weighed and the loss in weight indicated friability. The acceptance limits of weight loss should not be more than 1%. This test was performed to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting.

***Swelling Index*:** Swelling index of the prepared tablets was measured using dissolution test apparatus (USP apparatus II method) with 900 ml of phosphate buffer pH 6.8 as dissolution medium. The paddles were operated at 50rpm and temperature was maintained at 37±1º C throughout the experiment. Weight of the tablet was taken before the study (W1). The tablet was placed in the medium for predetermined time. The swollen tablets were removed, wiped and weighed (W2). The swelling index was calculated using the formula;

Swelling index = $\frac{W2-W1}{W1} \times 100$

***Drug Content Uniformity*:** Cilnidipine tablets from a batch were taken at random and were crushed to a fine powder. The powdered material was transferred into a 100 ml volumetric flask and few ml of methanol was added to it. It was shaken occasionally for about 30 minutes and the volume was made up to 100 ml by adding methanol. The resulting solution was set aside for few minutes and the supernatant solution was collected, filtered by using whattmann filter paper. Then the filtrate was subsequently diluted with phosphate buffer pH 6.8 and the absorbance was measured at 240 nm. This test was repeated six times (n=6) for each batch of tablets.

***In vitro Dissolution Studies of Cilnidipine Tablets*:** Dissolution studies for Cilnidipine tablet formulations were performed in a calibrated dissolution test apparatus (USP apparatus II method) using 900 ml of phosphate buffer pH 6.8 as dissolution medium. The paddles were operated at 50rpm and temperature was maintained at 37±1º C throughout the experiment. Samples were withdrawn at 0.5, 1, 2, 4, 6, 8, 10 and 12h and replaced with equal volume of same dissolution medium to maintain the constant conditions. The amount of drug dissolved was estimated using U.V spectrophotometer at 240nm. The dissolution profiles were given in (Figure 2).

Results and Discussion

Preparation of Cilnidipine Solid Dispersions by Solvent Evaporation Method: Solid dispersions of Cilnidipine were prepared using plasdone K-29/32 as carrier in different ratios by solvent evaporation method. The composition was given the Table 1.

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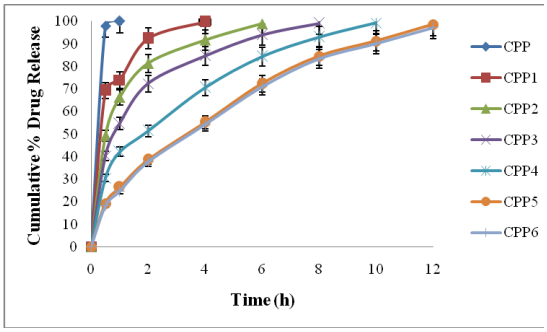

Fig 2. Dissolution Profiles of Cilnidipine Tablets

Mean ± S.D = Mean values ± Standard Deviation of three experiments

***Evaluation of Physical Parameters of Cilnidipine Solid Dispersions*:** Various physical parameters for Cilnidipine solid dispersions were evaluated. All the flow properties were found to be within I.P specified limits. The obtained results were indicated in table 2.

***In vitro* Dissolution Studies of Cilnidipine Solid Dispersions:** Formulation CP3, prepared using Cilnidipine and plasdone K-29/32 in 1:3 ratios showed maximum drug release. This showed that plasdone K-29/32 significantly increases drug release as suggested by past studies (16, 17). The dissolution profiles of Cilnidipine solid dispersions were given in Fig 1.

***Preparation of Cilnidipine Tablets*:** Cilnidipine tablets were prepared using the optimized solid dispersions (CP3) along with various concentrations of PEO WSR 303 by direct compression technique. The compositions were given in table 3.

***Evaluation of Pre-Compression Parameters*:** The pre compression parameter values obtained for various prepared granules were given in the table 4. The angle of repose, Carr's index and Hausner's ratio values for granules were within the range specified. Thus all the prepared granules were found to be stable and suitable for compression of tablets.

***Evaluation of Post Compression Parameters of Cilnidipine Tablets*:** The direct compression method was found to be suitable for preparation of controlled release tablets. Cilnidipine tablets were prepared and evaluated for post compression parameters. The results were given in table 5. Weight uniformity, hardness and friability loss of tablet formulations were within the specified limits.

***In vitro Dissolution Studies of Cilnidipine Tablets*:** Dissolution studies were carried on Cilnidipine tablets using U.S.P paddle method (apparatus II) with phosphate buffer pH 6.8 as dissolution medium by maintaining the bath temperature at 37±1°C and the paddles were operated at 50rpm. The dissolution profiles of tablets were given in Table 8. The study clearly indicated that increase in the concentration of PEO WSR 303 as polymer has slowed down the drug release in the prepared tablet formulations. Formulation CPP5 containing 25% w/w of PEO WSR 303 as polymer exhibited controlled and prolonged dissolution profile. Similar drug release profile was observed with CPP6 formulation which was made using 30% w/w of PEO WSR 303. Thus the results obtained strongly suggest the usage of PEO in controlled release formulations which matches with recent findings (18, 19). The results were shown in Fig 2.

Conclusion

The present study showed that proportion of polymers used in preparation of formulations has high impact on dissolution parameters. The formulation CPP5 prepared with Cilnidipine solid dispersions using Plasdone K-29/32 (1:3 ratios) and PEO WSR 303 (25%w/w) showed slower drug release.

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Conflict of Interest

Authors declare no conflict of interest.

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