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Research Article

Pharmaceutics for effective drug dosage

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

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ABSTRACT: Drug solubility plays an important role in the improvement of bioavailability. Biopharmaceutical Classification System (BCS) Class-II drugs have less solubility and more permeability. Most of the drugs available in the market belong to BCS class-II. The objective of the present study is to improve the solubility of BCS Class-II drug, Cilnidipine by formulating them as solid dispersions and to make controlled release 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 in a short time. The pre and post compression parameters of the solid dispersions and tablets were within specified limits. Formulation CPP5 containing CP3 solid dispersion with 25% w/w of PEO WSR 303 showed prolonged drug release up to 12h. Similar drug release was also obtained with CPP6 formulation having 30%w/w of PEO WSR 303. The present study prepared a novel Cilnidipine pharmaceutical product having increased solubility and prolonged drug release which is not available in the market. The solubility of Cilnidipine was enhanced using plasdone K-29/32 and the drug release was delayed using PEO WSR 303 as polymer. This could be advantageous to many of the patients with cardiovascular disorders.

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

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1. INTRODUCTION

Solubility is an important factor for any drug to show its pharmacological effect in the body. Nowadays, most of the drugs are facing the problem of aqueous solubility.[1]In such cases, solubility enhancement could be helpful which could be beneficial for many patients.[2] 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.[3] 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.[4] Solid dispersions dissolve drug in water by employing various mechanisms like making complexes, reducing the particle size, increasing wetting time.[5] 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.[6] Prolonged gastric retention of drug also increases bioavailability, decreases wastage of drug and improve solubility for drugs that are less soluble in a high pH environment.[7] This could be achieved by using certain polymers like polyethylene oxides.[8] Poly ethylene oxides are hydrophilic in nature and are available in various grades. They help in prolonged drug release.[9] PEO WSR 303 is one such water soluble swellable polymer which is employed in formulation of controlled release formulations that acts as release retarding agent.[10.] A lot of research work has been carried out on the preparation of solid dispersions and controlled release formulations separately.[11-14]. But a very little research has been carried out in the preparation of controlled release formulations made out of solid dispersions using various polymers. So, the rationale of this research is a need to develop a suitable formulation which could not only increase solubility of the drug, but also provides extended drug release. The novelty of the current study lies in making such a combined effective formulation. In the 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. This could change the solubility and drug release pattern of Cilnidipine. It shows the anti-hypertensive effect by blocking L-type calcium channels on blood vessels. It also suppresses the contraction of blood vessels.[15]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. The main aim of the current study is to enhance the solubility of Cilnidipine and also to prepare a controlled release formulation using suitable polymers. This study developed a novel pharmaceutical formulation that could be a boon to people suffering with cardiovascular problems who need to take the drugs in a regular manner.

2. MATERIALS AND METHODS

2.1 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 from S.D Fine Chem. Ltd. (Mumbai, India).

2.2 Methods

2.2.1. *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.[16] Measured quantities of Cilnidipine and Plasdone K-29/32 were placed in a china dish. Few ml of methanol was added and heated at low temperature until both melted. The mixture was allowed to evaporate by continuous stirring. The solid mass obtained after the solvent evaporation was crushed and stored in a desiccator for further study. The composition of various Cilnidipine solid dispersions was given in table 1.

2.2.2. *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.[17]The results were indicated in table 2.The angle of repose was measured to determine the flow properties. 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; Carr's Index is a simple test 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.

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

Hausner's ratio 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 was measured using sieves. 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 for the solid dispersions of Cilnidipine was measured by taking 10mg equivalent solid dispersions into a 100ml volumetric flask. To this, a 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 Whatman 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 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±1°C throughout the experiment. The samples were withdrawn at 5, 10, 15, 20 and 30min and replaced with equal volume of the same dissolution medium to maintain the sink conditions.[18]The amount of the drug dissolved in the dispersions was estimated by double beam UV spectrophotometer at 240nm. The dissolution profiles were indicated in figure 1.

2.2.3. *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 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.[19] The compositions of various tablet formulations were given in the table 3.

2.2.4. *Evaluation of Various Pre and Post compression Parameters for Cilnidipine Tablets*

The prepared granules were evaluated for pre compression parameters such as angle of repose, Carr's index and Hausner's ratio.[20] The results were given in table 4. The compressed tablets were further evaluated for post compression parameters such as weight uniformity, hardness, friability, swelling index and drug content.[21] The results were given in table 5.Weight uniformity was calculated by selecting twenty tablets randomly from a batch. They 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. 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 a 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 breaks the tablet. 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 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 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±1°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;

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

Drug content uniformity of Cilnidipine tablets was measured by taking tablets from a batch at random and crushing them to a fine powder. [22]This powder was then mixed with few ml of methanol in a 100 ml volumetric flask. The flask was shaken occasionally for 30 minutes. Finally using methanol, the volume was made up to 100 ml. This solution was kept aside for few minutes, filtered using whatman filter paper and the filtrate using pH 6.8 phosphate buffer was then diluted. The absorbance of the sample was measured at 240 nm. This test was repeated three times (n=3) for each batch of tablets[2]

2.2.5 *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±1°C throughout the experiment. Samples were withdrawn at 0.5, 1, 2, 4, 6, 8, 10 and 12h and replaced with equal volume of the same dissolution medium to maintain the constant conditions. The amount of drug dissolved was estimated using a UV spectrophotometer at 240nm. The dissolution profiles were given in figure 2.

3. STATISTICAL ANALYSIS

The results obtained were statistically presented as mean ± standard deviation (S.D) using Graph-Pad prism software (version 5.0). The hardness, weight uniformity, drug content and drug dissolution profiles were studied in triplicates.

4. RESULTS AND DISCUSSION

4.1 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. An increase in the concentration of plasdone K-29/32 was followed during the preparation of solid dispersions. Of all the methods in preparation of solid dispersions, solvent evaporation technique was quite famous and well used because of its highly positive rate in obtaining a desired formulation.[23] Usage of such techniques greatly lowers the particle size of the drug which leads to enhanced drug dissolution. The previous studies used plasdone K-29/32 as polymer for the preparation of solid dispersions.[24, 25] Proper incorporation of drug into the carrier also leads to increased bioavailability. The composition was given the table 1.

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*

4.2 *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. Of all the prepared solid dispersions, CP3 made using Cilnidipine and plasdone K-29/32 in 1:3 ratios has shown excellent flow properties. The standard deviation values obtained were within the low values of standard deviation. This indicated that the prepared solid dispersions exhibited good flow properties. Even the drug content in the solid dispersions indicated uniformity. Thus solvent evaporation technique is found to be reproducible for the preparation of solid dispersions. The obtained results were indicated in table 2.

Table 2: Physical Parameters of Cilnidipine Solid Dispersions

Solid Dispersion	Angle of Repose (^{0}) (Mean±S.D)	Carr's Index (%) (Mean±S.D)	Hausner's Ratio (Mean±S.D)	Average Particle Size (µm) (Mean±S.D)	Drug Content(mg) (Mean±S.D)
CD	32±1.24	22±0.81	1.30±0.01	42.33±1.05	09.64±0.98
CP1	23±0.81	21±1.63	1.22±0.02	188.33±1.86	10.04±0.47
CP2	21.33±0.47	17.33±0.94	1.19±0.02	172.34±2.04	09.99±0.63
CP3	20±0.81	12.33±1.25	1.15±0.02	155.66±1.24	10.08±0.31
CP4	21±0.82	14.33±1.25	1.18±0.01	164±1.63	09.95±1.03
CP5	23.33±0.47	15.33±1.24	1.20±0.01	169±2.44	10.11±0.32

**CD indicates Cilnidipine pure drug; Mean ± Standard deviation of three independent estimations*

4.3 *In Vitro Dissolution Studies Of Cilnidipine Solid Dispersions*

In vitro dissolution studies were performed for the prepared 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.[26, 27] It promotes the breakup of slugs into tiny fragments in an aqueous environment. It increases the available surface area and promotes rapid release of drug.[28-30] It is easily soluble in any type of solvent and can be used in preparation of any kind of solid dispersions for poorly water soluble drugs. It has high hydrophilicity and physiological stability which caused enhanced drug release.[31] It also prevents the drug crystallization by its anti-plasticizing effect that leads to increase in drug release.[32] The dissolution profiles of Cilnidipine solid dispersions were given in figure 1.

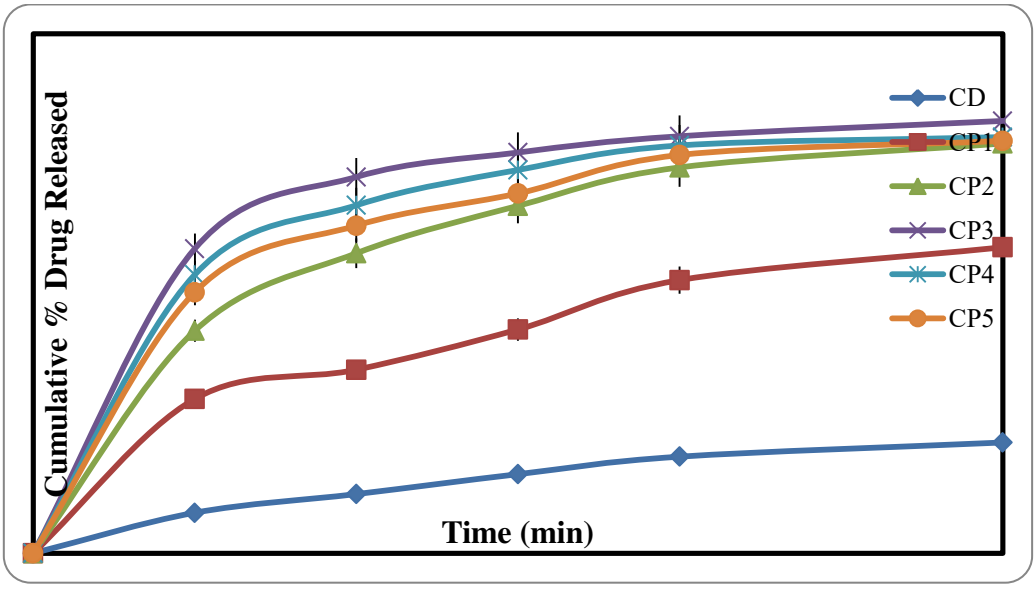

Fig 1: Drug Release Profiles of Cilnidipine Solid Dispersions
Mean ± Standard deviation of three independent estimations

4.4 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 formulation CPP doesn't contain any of the polymers. Formulations CPP1 to CPP6 contains PEO WSR 303 in increasing concentrations form 5%w/w to 30%w/w. PEO WSR 303 is one of the best polymers used in the preparation of controlled release formulations and is supported by the recent research.[33, 34] PEO generally acts by taking water when it comes in contact with the gastric fluid. The polymer chains undergo hydration and later gets disentangled. But, PEO WSR 303 is a high grade polymer with higher molecular weight and viscosity. It shows high resistance for the disentanglement which causes slower and delayed breakage of polymer chains.[35] Thus, the amount of PEO WSR 303 employed in the preparation of tablets greatly influences the later parameters. The compositions were given in table 3.

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

4.5 Evaluation Of Pre-Compression Parameters

The pre compression parameter values obtained for various prepared granules were given in table 4. The angle of repose, Carr's index and Hausner's ratio values for granules were within the range specified. Very less deviation of the pre compression parameters of the powder indicated better flow properties of the formulations which help in proper tablet formation. Thus all the prepared granules were found to be stable and suitable for compression of tablets.

Table 4: Pre-Compression Parameters of Cilnidipine Granules

Formulation	Angle of Repose (^{0}) (Mean±S.D)	Carr's Index (%) (Mean±S.D)	Hausner's Ratio (Mean±S.D)
CPP	31.33±1.25	21.00±1.44	1.22±0.02
CPP1	26.66±1.69	19.66±1.25	1.18±0.02
CPP2	24.33±1.08	17.00±1.63	1.17±0.02
CPP3	23.11±1.24	16.33±1.24	1.15±0.01
CPP4	22.00±1.63	14.66±1.70	1.13±0.02
CPP5	21.00±0.82	12.00±0.81	1.12±0.02
CPP6	20.66±0.94	11.66±1.24	1.12±0.02

Mean ± Standard deviation of three independent estimations

4.6 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. The friability values were very less which indicated the strength of the tablets. The drug content in the prepared tablets exhibited very less deviation. This indicated uniformity of drug disposition in the prepared Cilnidipine tablets. As the concentration of PEO WSR 303 increased, the swelling index also increased. Due to high viscosity of PEO WSR 303, the degree of swelling was high. Maximum swelling was observed for the formulation CPP6 with 30%w/w PEO WSR 303. It also has a special property of mucoadhesion which helps in prolonged gastric retention of the formulation.[36]

Table 5: Post Compression Parameters of Cilnidipine Tablets

Formulation	Weight Uniformity* (mg) (Mean ± S.D)	Hardness (kg/cm^2) (Mean ± S.D)	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

Mean ± Standard deviation of three independent estimations

4.7 *In Vitro Dissolution Studies Of Cilnidipine Tablets*

Dissolution studies were carried out 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 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. These results were in par with the other research findings where PEO WSR is employed in formulation of controlled release formulations.[37, 38] PEO being a hydrophilic polymer rapidly hydrates and forms a gel barrier around the outer layer of the drug. As the grade used in the current study is of high molecular weight (303), it provides delayed drug release via the hydrophilic matrix formation.[39] 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.[40-42].The results were shown in figure 2.

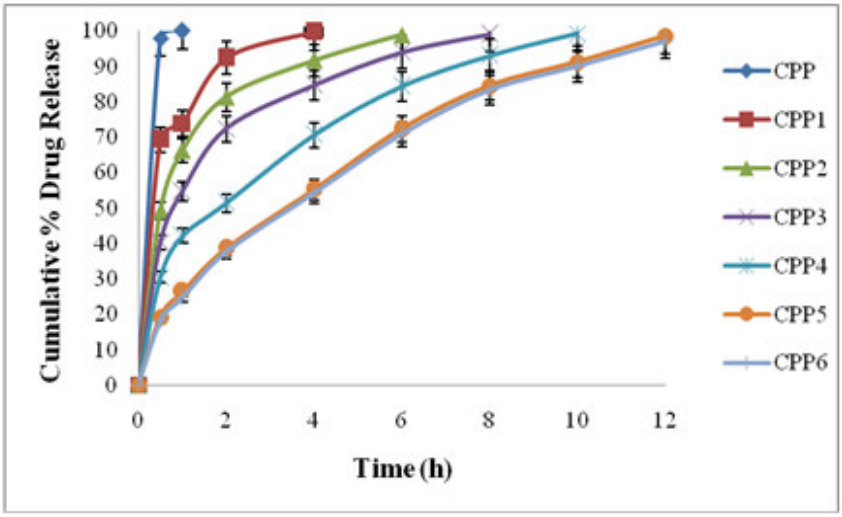

Fig 2: Dissolution Profiles of Cilnidipine Tablets

Mean ± S.D = Mean values ± Standard Deviation of three independent estimations

5. CONCLUSION

The present study showed that the proportion of polymers used in preparation of formulations has a high impact on dissolution parameters. Plasdone K-29/32 has greatly increased the aqueous solubility of Cilnidipine at the ratio of 1:3 of drug to polymer. Thus, plasdone K-29/32 can be used for solubility enhancement which is beneficial in case of BCS class-II drugs. Whereas PEO WSR 303 caused prolonged drug release with its increase in concentration from 5% to 30%. Application of such polymer in preparation of any type of controlled release formulations is beneficial. 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. Thus this novel formulation could be a boon for many of the cardiac patients in a way that they need to take only one dose instead of multiple. This prevents loss of dose by the patient and helps in achieving better therapeutic result especially in case of geriatrics with cardiac issues. In future, this study could be recommended further for the evaluation of various pharmacokinetic parameters on animals.

6. ACKNOWLEDGEMENTS

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7. AUTHORS CONTRIBUTION STATEMENT

Mr. Ramakrishna Vydana and Dr. Chandra Sekhar Kothapalli Bonnoth conceptualized and designed the work process. Mr. Ramakrishna Vydana collected, analyzed, interpreted the data and drafted the manuscript. Dr. Chandra Sekhar Kothapalli Bonnoth contributed in editing and revising the manuscript. The authors have read and approved the final version of the manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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