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Research Article

Comparative Study Of Marketed Formulations Of Cilnidipine With Nexovas Tablet

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ABSTRACT

Hypertension could be a medical state in which blood pressure is chronically prominent. It is considered as the silent killer. Blood pressure is deliberated by the quantity of blood the heart pumps and therefore the quantity of resistance to blood flow within the arteries. The excess blood the heart pumps and therefore they narrower the artery, higher is the blood pressure. It is used for the treatment of cardiovascular disease. The method is predicted simultaneous equation for analysis of drug using methanol as solvent. Cilnidipine has absorbance maxima at 240nm in methanol. The dissolution tests were performed by employing USP type-II apparatus (Paddle type) at 50rpm using distilled water with 0.1% SLS and 0.1N HCl as dissolution media. The percentage cumulative release of Cilnidipine was measured for 6 hours respectively. None of the commercial brands were similar to Nexovas in dissolution profile. Nexovas tablets at both the strengths showed consistently higher release suggesting its pharmacokinetic activity could perhaps superior to other marketed brands of Cilnidipine as it would release the drug consistency.

INTRODUCTION

Hypertension or High Blood Pressure (140/90 mmHg or higher) and also known as Silent Killer

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are a medical state in which blood pressure is chronically prominent. If it is untreated lead to major health issues and higher risk of heart failure, heart attack, stroke and death. Blood pressure is measured by the number of blood the heart pumps and there for the quantity of resistance to blood flow within the arteries.[1] International and National guidelines briefly describes Anti-hypertensive drug treatment which includes Angiotensin II receptor blockers, Angiotensin converting enzyme inhibitors (ACE), α-blockers, β-blockers, Central agonists, Organic calcium channel blockers and Diuretics all these are used to treat high blood pressure and other disease condition related to heart. All these anti-hypertensive agents have some limits, indications and good therapeutic response for any disease as per individual patient.[2]

Drug Profile:

Cilnidipine is a promising fourth generation calcium channel blocker, dual L/N-type dihydropyridine calcium channel blocker (also known as calcium antagonists), variety of new antihypertensive moderator.[3]

Cilnidipine is a diesterified 1, 4-dihydropyridine-3, 5-dicarboxylic acid that reduces the hypertensive action.[4] It acts on L-type calcium channels by blocking incoming calcium and suppressing the concentration of blood vessels. It also acts on N-type calcium channels by inhibiting emission of norepinephrine and suppressing then higher stress blood pressure.[5] Cilnidipine classified in Biopharmaceutical Classification System Class-II type drug. Therefore, Cilnidipine has low solubility and high permeability. It shows rapid absorption with maximum peak concentration after 2 hours.[6] The movement and study of the absorption, distribution, metabolism and excretion of drugs is known as pharmacokinetics (PK). The connection between concentrations or dose of drug and pharmacological or toxicological effects, particularly how solid dosage forms are absorbed in vivo, is known as pharmacodynamics (PD).[7] The pharmacokinetic and pharmacodynamics characteristics are excellent indicators to shows good therapeutic response.[8, 9] In this process many complicated factors are involved, among which, drug disintegration and dissolution are very important ones.[10] Formulations of different brands have different types and amount of diluents, disintegrates, lubricants, or other excipients. They may be also being exposed to various compression forces which impact the rate of disintegration and dissolution of a particular formulation. Apart from this, feedback from doctors that some Cilnidipine brands need to be given more than the recommended once daily dose or that doses higher than the recommended 10 mg are required to produce the desirable clinical effects necessitated a study comparing the dissolution profiles and other parameters of these generic Cilnidipine formulations with that of the Nexovas tablet.

MATERIALS AND METHODS:

Samples:

Four commercially available samples were purchased from the local market for the study.

Table 1: Marketed formulations of Cilnidipine

Sr. No.	Name	Dose	Company	Batch no.	Mfg. date	Exp. date
1	Cilacar	5mg	Unique	KCB21004	Mar. 2021	Feb. 2024
		10mg		KC921003	Feb. 2021	Jan. 2024
2	Cilnilyy	5mg	Helios	20S1GTA228	Aug. 2020	Jul. 2022
		10mg		20S1GTA554	Dec. 2020	Nov. 2022
3	Cilnidib	5mg	Prevego	MT194353	Mar. 2020	Feb. 2022
		10mg		MT211137A	Mar. 2021	Feb. 2023
4	Cilogard	5mg	Cipla	GC920002	Jan. 2020	Dec. 2021
		10mg		GD130004	Jun. 2020	May 2022
5	Nexovas	5mg	Macleods	KNB2004A	Jun. 2020	May 2022
		10mg		KNA911A	Dec. 2019	Nov. 2021

Chemicals:

1. Cilnidipine (J. B. Chemicals, Mumbai, India).
2. Concentrated hydrochloric acid, Sodium lauryl Sulphate, Methanol (Research Lab, fine chemical industries, Mumbai, India).
3. Whatmann Filter Paper (Ash less, 1440-110, Grade 40 circles, 110 mm)
4. Distilled water

Apparatus/Instruments:

Dissolution Test Apparatus

- USP type II apparatus (Paddle)
- Electro lab Tablet Dissolution Tester USP TDT-06

UV Visible Spectrophotometer

- Shimadzu UV-1560

Monsanto Hardness Tester

- Model: EI 66 Expo

Disintegration Test Apparatus

- Electro lab tablet disintegration tester USP, ED-22

Experimental Work:

- All samples were coded as shown in Table 1 and submitted to the investigator for analysis.
- All products tested were stored within specific condition and within their shelf life.

Analytical Method Development:

For dissolution study, the drug was analyzed by UV Spectroscopy at λ max of 240nm and standard curves were plotted for respective buffers.

Standard Calibration Curve of Cilnidipine in Methanol:

Preparation of stock solution of Cilnidipine:

10mg of Cilnidipine was accurately weighed and placed to a 100ml volumetric flask. To generate a stock solution of 100µg/ml, the medication was dissolved in methanol and the volume was increased to 100ml.

Calibration Curve of Cilnidipine in Methanol:

Different aliquots of this solution were diluted to get solutions with Cilnidipine concentrations of 2, 4, 6, 8, 10, 12 and 14µg/ml. On a UV-Visible spectrophotometer, the absorbance of these solutions was measured at 240nm against methanol as a blank. A graph of absorbance versus corresponding concentrations was plotted to establish linearity over the whole concentration range. Linear regression analysis was used to statistically examine the data.

Standard Calibration Curve of Cilnidipine in 0.1N HCI:

Preparation of stock solution of Cilnidipine:

10mg of Cilnidipine was accurately weighed and placed to a 100ml volumetric flask. To generate a stock solution of 100µg/ml, the medication was dissolved in 0.1N HCI and the volume was increased to 100ml. For 15 minutes, the stock solution was maintained in an ultra sonicator. The

solution was then filtered using a Whatmann paper 0.41 filter.

Calibration Curve of Cilnidipine in 0.1N HCI:

Different aliquots of this solution were diluted to get solutions with Cilnidipine concentrations of 2, 4, 6, 8, and 10µg/ml. On a UV-Visible spectrophotometer, the absorbance of these solutions was measured at 240nm against a blank of 0.1N HCI. A graph of absorbance versus corresponding concentrations was plotted to establish linearity over the whole concentration range. Linear regression analysis was used to statistically examine the data.

Standard Calibration Curve of Cilnidipine in distilled water with 0.1% SLS:

Preparation of stock solution of Cilnidipine:

10 mg of Cilnidipine was accurately weighed and placed to a 100ml volumetric flask. To obtain a stock solution of 100g/ml, the medication was dissolved in distilled water with 0.1% SLS and the volume was increased to 100ml. For 15 minutes, the stock solution was maintained in an ultra sonicator. The solution was then filtered using a Whatmann paper 0.41 filter.

Calibration Curve of Cilnidipine in distilled water with 0.1% SLS:

Different aliquots of this solution were diluted to get solutions with Cilnidipine concentrations of 2, 4, 6, 8, and 10µg/ml. On a UV-Visible spectrophotometer, the absorbance of these solutions was measured at 240nm against a blank of distilled water with 0.1% SLS. A graph of absorbance versus corresponding concentrations was plotted to establish linearity over the whole concentration range. Linear regression analysis was used to statistically examine the data.

Evaluation Parameters:

Weight Variation:

To check for weight variance, ten tablets were chosen at random from each batch and weighed individually. According to the United Stated Pharmacopoeia, a little variation in the weight of the tablets was performed. The values for weight variations are provided in the table 2.

Hardness:

Hardness signifies the capacity of a tablet to endure mechanical shocks while handling. A Monsanto hardness tester was used to determine the hardness of tablets. It is expressed in kg/cm2. The values for hardness are provided in the table 2.

Friability Test:

The Roche Friabilator was used to friability of the tablets. It is expressed in percentage (%). For tables with an average weight of 5mg and 10mg tablets accurately weighed the initial weight of tablets and place the tablets in friabilator drum. The friabilator was carry at 25 rpm for 4 minutes or run up to 100 revolutions and remove the tablets and remove any loose dust and weight the final weight accurately.

$$\% \text{ Friability} = \frac{\text{Initial weigth-Final weight}}{\text{Initial weight}} \times 100$$

The percent friability was then calculated by-

% friability of tablet less than 1% was considered acceptable. The values for friability are provided in the table 2.

Disintegration Test:

A tablet was placed in each of the six tubes of the apparatus and a disc was added to each tube. The discs help to ensure submersion of the dosage unit and the necessary surface wetting to facilitate disintegration. Then it was suspended into 1000ml glass beaker containing 900ml of distilled water maintained at temperature of 37 ± 2°C. The time taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds. The values for disintegration test are provided in the table 2.

Drug Content:

The formulation equivalent to 5mg and 10mg tablet powder of each batch was weighed transferred in 100ml volumetric flask and diluted

suitably with methanol. From the stock solution take first dilution of each batch. The absorbance was measured at 240nm and the amount of drug in each formulation was calculated. The values for drug contents are provided in the table 2.

Dissolution Test:

Dissolution studies were performed using USP Dissolution apparatus type II (paddle type) with 900ml. 0.1N HCI and distilled water with 0.1% SLS as dissolution medium. All studies were carried out at 37±0.5ºC, 50 rpm speed for 6 hours at time intervals 10ml aliquots were withdrawn, filtered each with whatmann filter paper. To maintain constant volume during the test time, equivalent quantities of new dissolving media were supplied as replacement. The amount of drug present in each sample was determined by UV-Visible spectrophotometer at 240nm.

Kinetic release of dissolution data with different models:

Pharmacokinetic and pharmacodynamics modeling and simulation play an important part in the drug development process, assisting in the generation of hypothesis, interpretation and understanding of experimental and trial results, integration of data and translate it to clinical implications. Thus, a modeling and simulation facility decision-making at each stage of drug development and helps to efficiently shape the next step.[11, 12]

Data Analysis (Curve Fitting Analysis):[13, 14]

- Cumulative percentage drug released versus time (in vitro drug release plots)
- Cumulative percentage drug released versus square root of time (Higuchi plots)
- Log cumulative percentage drug remaining versus time (First order plots)
- Log percentage drug released versus log time (K. Peppas plots)

Zero Order Release Model:

It defines a linear relationship between the fractions of drug release versus time.

$$Q = K_0 t$$

Where,

Q is a fraction of drug released at time t.

K0 is the zero order release rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.[15,16]

First Order Release Model:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablet could be described adequately by apparent first order kinetics. The equation that describes first order kinetics is in.

$$(1-Q) = -K_1 t$$

Where,

Q is the fraction of drug released at time t.

K1 is the first order release rate constant. Thus, a plot of the logarithm of the drug undissolved against time will be linear if the release obeys first order release kinetics.[17]

Higuchi Model:

It defines a linear dependence of the active function released per unit of surface (Q) the square root of time.

$$Qt = K_2 t^{1/2}$$

Where,

K2 is the release rate constant.

If the release obeys higuchi equation, a plot of the fraction of drug released against square root of time will be linear. The data obtained from in vitro release studies were plotted as cumulative drug percent release versus square root of time.[18]

Korsemeyer – Pappas Release Model:

To describe the drug release behavior from polymeric systems, the dissolution data were also fitted according to the well-known exponential Korsmeyer-Peppas equation.

$$(Qt/Q\infty = Ktn)$$

Where,

Qt is the fraction of drug release at time t.
k is the kinetic constant.
n is the exponent (indicating the general operating release mechanism).

For tablets, depending on the aspect ratios, n value between 0.43 and 0.5 indicating fiction (case I) diffusion-mediated release, non-Fiction (Anomalous) release, coupled diffusion and polymer matrix relaxation occurs of 0.5<n<0.89, purely matrix relaxation or erosion-mediated release occurs for n=1 (zero order kinetics) and super case II type of release for n>0.89.[19, 20]

Hixson Crowell Model:

The data obtained from in vitro release studies were plotted as cube root of percent of drug remaining versus time.[21]

Similarity Factor and Difference Factor:

In order to compare the dissolution profiles, using mathematical methods with equation f1 (difference factor), f2 (similarity factor). Factors f1 and f2 were calculated according to the criteria. The difference factor (f1) gives the percentage difference between two curves at each reading time and is a measure of the relative error between the two curves. On the other hand, the similarity factor (f2) is the most appropriate method to compare release profiles. The difference factor (f1) gave values within the specified limits 0-15 and the similarity factor (f2) was close to 50. The comparison of dissolution profiles using f1 and f2 is simple to grasp, produces consistent findings and also widely used due to approved by the FDA.

"f2 = 50log" {["1" /"T" ∑_"t=1" ^"T" ▒("Xt-Yt")"2"]"-0.5X100" }

Xt is dissolution percentage of reference at time t and Yt is dissolution percentage of samples at time t.[22]

RESULT:

Analytical Method Development:

Standard plots of Cilnidipine and their respective equations relating the concentrations and absorbance were plotted. The method was found to be linear in the range of 2-14µg/ml with a regression coefficient closed to 0.999. The slope of equation was shown to be consistent in all the developed methods.

Evaluation Parameters:

Table 2: Evaluation parameters for marketed formulations of Cilnidipine and Nexovas

Sr. No.	Name	Strength	Weight Variation	% Friability	Assay	Hardness (mg/kg)	DT (sec)
1	Cilacar	5mg	94±2	0.5±1	97.5	2.5	30
		10mg	126±4	0.2±0.8	92.73	2.8	35
2	Cilnilyy	5mg	196±3	0.3±0.6	81.81	0.6	34
		10mg	293±5	0.6±1	84.47	2	35
3	Cilnidib	5mg	179±6	0.5±0.8	63.86	5	40
		10mg	184±3	0.8±1	69.73	1.8	37
4	Cilogard	5mg	176±4	0.4±0.8	88.75	6.8	42
		10mg	175±3	0.6±0.9	89.78	8	38
5	Nexovas	5mg	72±5	0.4±0.7	99.89	4.2	40
		10mg	145±3	0.6±1	100	3.4	45

Dissolution Study:

The drug release of marketed formulations of Cilnidipine (5mg and 10mg) and Nexovas tablets (5mg and 10mg) in dissolution medium such as 0.1N HCI and Distilled water with 0.1% SLS were performed by using dissolution apparatus. The obtained results were shown in the table 3, 4, 5, and 6 which contains percentage drug release data

of Nexovas tablets and marketed formulation of Cilnidipine such as Cilacar, Cilnilyy, Cilnidib and Cilogard from 30-360 minute in the selected dissolution medium. The graphical representation of drug release were shown in the figure 1, 2, 3 and 4 for Nexovas tablets and marketed formulation of Cilnidipine such as Cilacar, Cilnilyy, Cilnidib and Cilogard with complete drug release profile.

Drug release of marketed formulations of Cilnidipine 5mg tablets in dissolution medium of 0.1N HCl:

Table 3: Cilnidipine 5mg tablets dissolution in 0.1N HCl

Sr. No.	Time (min)	Cilacar	Cilnilyy	Cilnidib	Cilogard	Nexovas
1	30	18.61	20.01	15.43	20.70	28.48
2	60	20.24	27.80	18.41	26.42	31.69
3	120	27.34	37.87	22.76	45.66	37.64
4	180	43.37	46.80	28.71	50.47	52.99
5	240	46.80	51.38	46.80	66.73	69.25
6	300	56.88	60.09	59.63	67.64	87.80
7	360	60.54	69.93	66.27	68.33	97.41

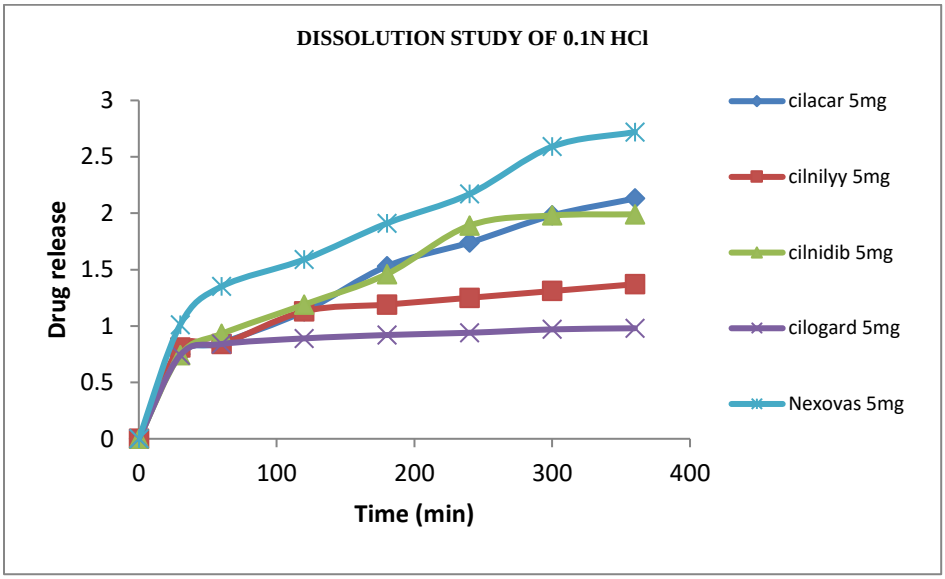

Figure 1: Graphical representation of dissolution profile of various brands of Cilnidipine 5 mg tablets in 0.1N HCl

Drug release of marketed formulations of Cilnidipine 10mg tablets in dissolution medium of 0.1N HCl:

Table 4: Cilnidipine 10mg tablets dissolution in 0.1N HCl

Sr. No.	Time (min)	Cilacar	Cilnilyy	Cilnidib	Cilogard	Nexovas
1	30	12.22	13.60	20.93	10.39	31
2	60	20.93	23.67	22.99	22.76	36.50
3	120	35.35	36.73	38.79	35.35	46.80
4	180	46.35	46.12	44.74	45.20	68.10
5	240	50.01	55.74	51.38	50.93	80.70
6	300	67.57	61.92	52.99	58.03	87.80
7	360	80.96	66.50	61.46	65.35	96.73

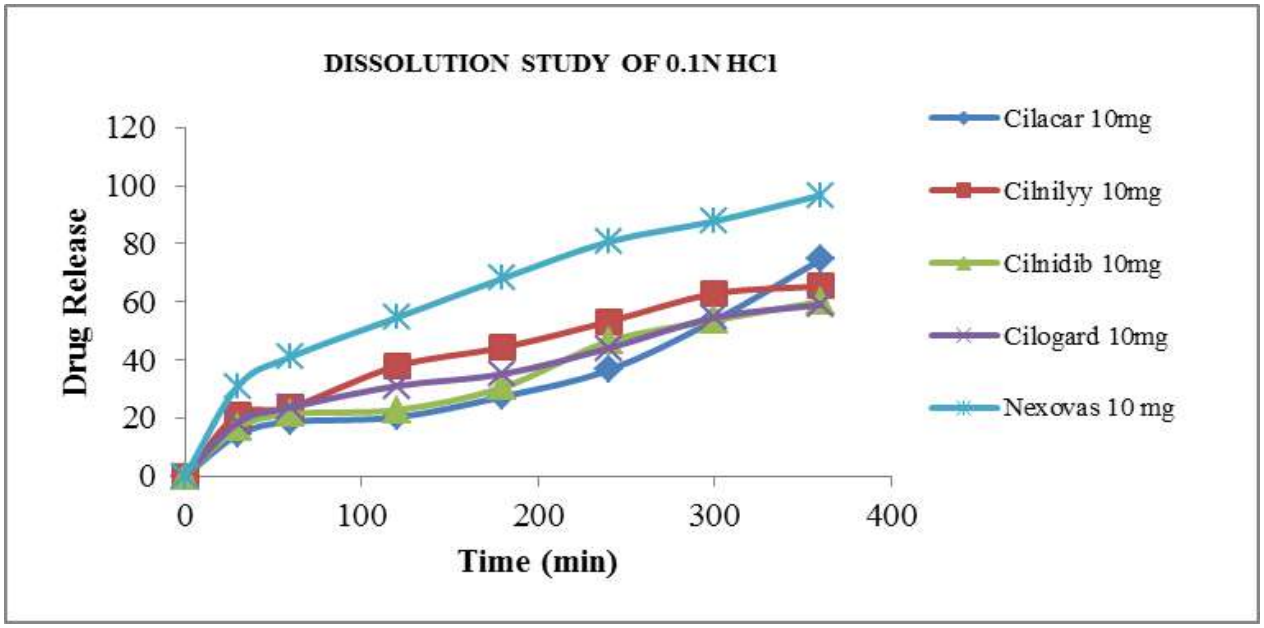

Figure 2: Graphical representation of dissolution profile of various brands of Cilnidipine 10 mg tablets in 0.1N HCl

Drug release of marketed formulations of Cilnidipine 5mg tablets in dissolution medium Distilled water with 0.1% SLS solution:

Table 5: Cilnidipine 5mg tablets dissolution in distilled water with 0.1% SLS solution

Sr. No.	Time (min.)	Cilacar	Cilnilyy	Cilnidib	Cilogard	Nexovas
1	30	21.84	18.87	14.29	18.41	28.71
2	60	31.92	29.17	24.13	21.84	35.58
3	120	36.73	32.15	27.57	30.54	51.16
4	180	44.74	42.22	35.35	36.27	65.81
5	240	50.93	42.91	38.33	45.66	78.41
6	300	55.74	46.58	44.29	51.16	90.09
7	360	65.35	54.59	45.43	58.48	95.12

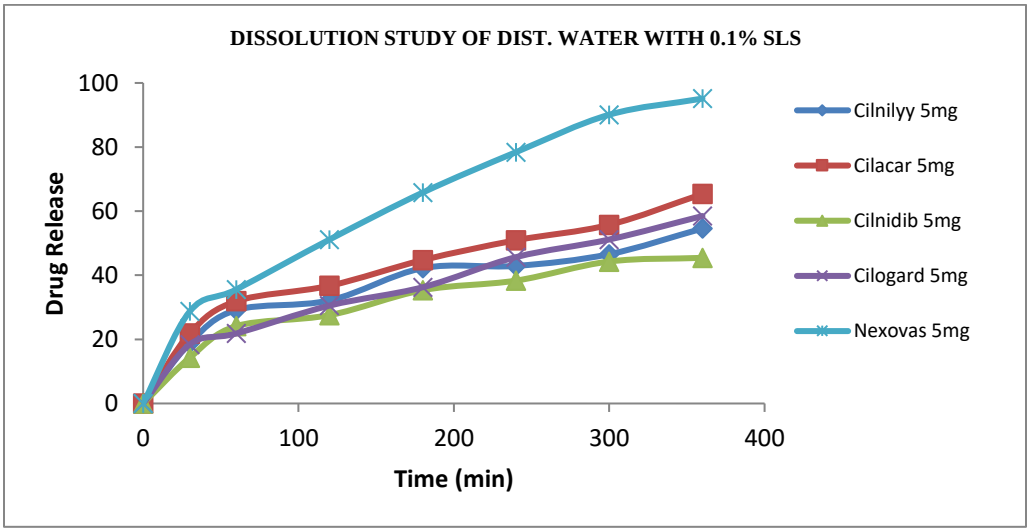

Figure 3: Graphical representation of dissolution profile of various brands of Cilnidipine 5 mg tablets in distilled water with 0.1% SLS solution

Drug release of marketed formulations of Cilnidipine 10mg tablets in dissolution medium of distilled water with 0.1% SLS:

Table 6: Cilnidipine 10 mg tablets dissolution in distilled water with 0.1% SLS

Sr. No.	Time (min.)	Cilacar	Cilnilyy	Cilnidib	Cilogard	Nexovas
1	30	14.29	21.16	16.58	18.41	29.63
2	60	18.64	28.25	21.38	23.67	40.16
3	120	20.24	37.87	22.76	31	51.38
4	180	27.34	44.29	30.54	35.12	63.52
5	240	36.50	53.22	46.35	44.06	85.28
6	300	53.67	62.83	53.67	54.59	90.09
7	360	65.35	69.25	60.09	58.94	96.27

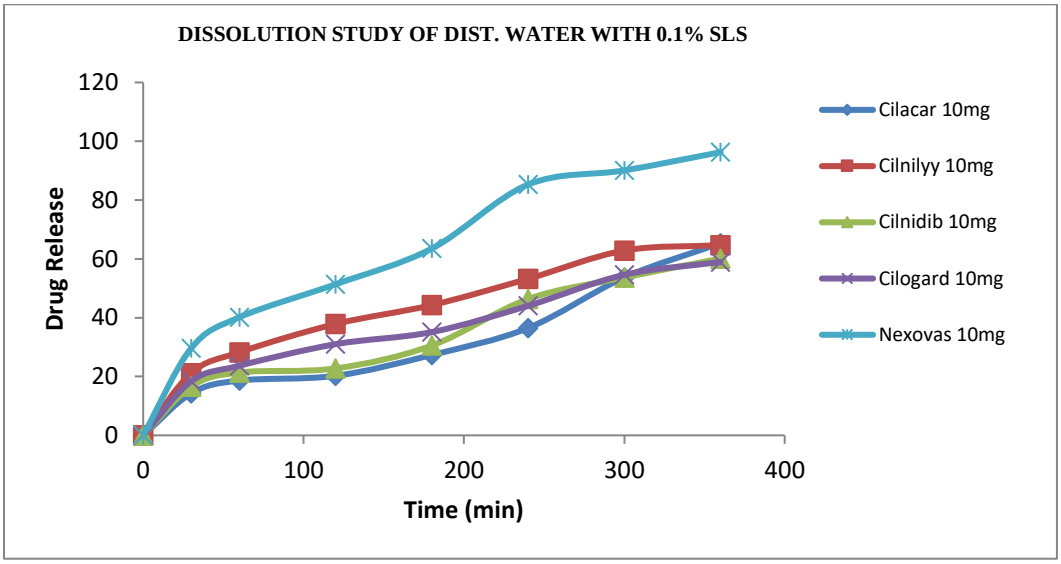

Figure 4: Graphical representation of dissolution profile of various brands of Cilnidipine 10 mg tablets in distilled water with 0.1% SLS solution

Kinetic Model Study:

The study of dissolution kinetics means determination of bioavailability of selected drug such as Nexovas and marketed formulations of Cilnidipine. The applied kinetic model were shown in table 7 and 8 for marketed formulations of Cilnidipine and Nexovas in 0.1N HCI and Distilled water with 0.1% SLS. Similarity and Difference factor is a type of model independent approach based upon mathematical equation for comparison of two dissolution profiles. After calculation, the obtained result were shown in table 9 as f1 values represent percent relative error between two curves on all time points. And f2 values represent similarity in percent dissolution between two curves.

Kinetic model study for marketed formulations of Cilnidipine (5mg and 10mg) and Nexovas in 0.1N HCl:

Table 7: Kinetic model study for marketed formulations of Cilnidipine and Nexovas in 0.1N HCl

Sr. No.	Name	Strength	Best fitted model
1	Cilacar	5mg	First order
		10mg	Hixon crowel
2	Cilnilyy	5mg	Higuchi model
		10mg	First order
3	Cilnidib	5mg	Zero order
		10mg	Higuchi model
4	Cilogard	5mg	Higuchi model
		10mg	Higuchi model
5	Nexovas	5mg	Higuchi model
		10mg	Higuchi model

Kinetic model study for marketed formulations of Cilnidipine (5mg and 10mg) and Nexovas in distilled water with 0.1% SLS:

Table 8: Kinetic model study for marketed formulations of Cilnidipine and Nexovas in distilled water with 0.1% SLS

Similarity factor and Difference factor:

Table 9: Similarity factor and Difference factor

Sr. No.	Name	Strength	Result			
			0.1N HCl		0.1% SLS Solution	
			f1	f2	f1	f2
1	Cilacar	5mg	33	33	32	32
		10mg	35	30	24	49
2	Cilnilyy	5mg	39	23	27	40
		10mg	33	32	33	31
3	Cilnidib	5mg	33	37	24	49
		10mg	30	35	26	45
4	Cilogard	5mg	42	10	27	41
		10mg	31	36	27	42

DISCUSSION:

When a tablet is ingested it undergoes disintegration, disaggregation and dissolution before being absorbed, the rate and extent of which into the systemic circulation determination determines its bioavailability. The solubility of a drug is key determinants to its oral bioavailability being the rate-limiting step to absorption of drugs from the gastrointestinal tract. As a result of low solubility, low bioavailability and significant inter, intra subject variance and huge changes in blood drug concentrations under fed versus fasting circumstances ensure. Time at the absorption site may be insufficient if the medication does not dissolve quickly or does not permeate the epithelial barrier. This research describes easy, susceptible, quick, correct, specific and economical spectrometric method based on evaluation of Cilnidipine. The method is predicted simultaneous equation for analysis of drug using methanol as solvent. Cilnidipine has absorbance maxima at 240nm in methanol. The linearity was obtained in concentration range 2-14µg/ml for Cilnidipine. The LOD value was found to be

0.355µg/ml and LOQ value found to be 1.08µg/ml. The mean recovery was 100.39% respectively. The relative standard deviation found to be <2.0%. The present result shows that the proposed method can be successfully used for simultaneous determination of drug content in marketed formulations. The melting point of Cilnidipine was found to be 115.5 to 116.6ºC. The solubility of Cilnidipine was done. It is freely soluble in methanol, ethanol and sparingly soluble in water. It complies with the identification test as per specifications. The weight variation of the all tablets not varied than 0.5mg of each tablet. The % friability was determined by Roche friabilator and all the marketed preparations of Cilnidipine comply with the specification limit 1%. Higher drug content observed in Nexovas tablets (both strengths). The Disintegration time for all the formulations found in between 30 to 40 sec. The dissolution tests were performed by employing USP type-II apparatus (Paddle type) at 50rpm using distilled water with 0.1% SLS and 0.1N HCl as dissolution media. The percentage cumulative release of Cilnidipine was measured for 6 hours respectively. The factor f2 of the FDA's SUPAC Guide was applied to the qualitative determination of 'similarity' between pairs of dissolution profiles of Nexovas and those of each investigated formulation. None of the commercial brands were similar to Nexovas in dissolution profile. This was observed for both strengths. Nexovas tablets at both the strengths showed consistently higher release suggesting its pharmacokinetic activity. Mostly this investigation shows the Higuchi model in the marketed formulations of Cilnidipine.

CONCLUSION:

From the above research, a Nexovas tablet (5mg and 10mg) was compared with commercial tablets of Cilnidipine such as Cilacar, Cilnilyy, Cilnidib and Cilogard. Nexovas and commercial tablets of Cilnidipine were evaluated for each test and ranges founds in the limit as per Indian Pharmacopeia. The Higher variability has seen during dissolution within the Nexovas tablets and commercial tablets. Also, different types of drug release kinetic models were applied to study release of dissolution within the marketed formulations of Cilnidipine. And difference factor, similarity factor were applied to optimize the dissolution profile in between Nexovas and commercial tablets. Thus, the present research on comparative study of Nexovas tablets and marketed formulations of Cilnidipine demonstrates for improved bioavailability and better patient compliance.

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