

Application of Novel Natural Sweetening Agent-Stevia in Formulation, Evaluation of Nicardipine Hydrochloride Orodispersible Tablets for Rapid Absorption

Nagasen Dasari^{1,2,*}, Chirravuri Satyanarayana Phani Kumar^{1,2}, Rama Krishna Gummadi^{1,2}, Sai kiran Pindiprolu^{1,2}, Sujiya Balla^{1,2}, Amala Masa³, Lavanya pulidindi⁴, Vajrapu Subhaveera Prasanth^{1,2}

¹Aditya Pharmacy College, Surampalem, Andhra Pradesh, INDIA.

²Jawaharlal Nehru Technological University Kakinada, Kakinada, Andhra Pradesh, INDIA.

³Department of Pharmacology, Krishna University College of Pharmaceutical Science and Research, Machilipatnam, Krishna, Andhra Pradesh, INDIA.

⁴Department of Horticulture, East Godavari, Andhra Pradesh, INDIA.

ABSTRACT

Objectives: The objective of this study was to develop a stable and effective form of an Orodispersible tablet containing Nicardipine Hydrochloride for the immediate treatment of high blood pressure and angina. The aim was to achieve this by using the natural sweetener stevia to improve taste. **Background:** Nicardipine Hydrochloride is used to treat high blood pressure and angina. However, currently available immediate release forms have limitations in terms of drug release and taste. Therefore, the goal was to develop an Orodispersible form of the drug that would enhance drug release and improve taste masking capabilities. **Materials and Methods:** We developed formulations of Nicardipine Hydrochloride Orodispersible tablets using the natural sweetener *Stevia rebaudiana* to enhance taste and reduce the caustic sensation. We confirmed the compatibility of the drug-exipient mixture using FTIR. Drug content and dissolution were determined through UV spectrophotometry. We also conducted organoleptic tests and other compendial specification tests. Precompression parameters were evaluated, and measures were taken to improve the flow behavior of the formulation blend by using excipients with excellent flow properties. Based on disintegration and dissolution time, we selected the F6 formulation as the optimized formula. We then subjected the developed trial to stability studies for three months, evaluating disintegration time, drug content, and dissolution. **Results:** The optimized formulation demonstrated a disintegration time of 46.25 ± 0.85 sec and a dissolution rate of 100.50 ± 2.50 . Compendial tests remained stable without any significant fluctuations after the stability study. Also, the taste of the drug was pleasant after taste. **Conclusion:** Through the appropriate selection of excipients, we successfully developed a stable and effective form of Nicardipine Hydrochloride Orodispersible tablet with enhanced drug release (using the solid dispersion technique) and improved taste masking capabilities. The optimized formulation yielded favorable results in terms of disintegration and dissolution time, drug content, and stability.

Keywords: Orodispersible tablets, *Stevia rebaudiana* FTIR, UV spectrophotometry, Angina pectoris.

Correspondence:

Mr. Nagasen Dasari

Assistant Professor, Aditya Pharmacy College, Surampalem, Kakinada-533437, Andhra Pradesh, INDIA.
Email: nagasenpharma@gmail.com

Received: 25-01-2023;

Revised: 09-02-2023;

Accepted: 03-11-2023.

INTRODUCTION

'Orodispersible Tablet' can be interpreted as "uncoated unit dosage form used for buccal or oral cavity, where it disperses prior to consumption" appears in Pharmacopoeia (European). They resolve the complications with desirable advantages associated with conventional dosage forms, and it has desired advantages

like hardness, uniformity of dosage, extremely easy way of administration as no solvent is necessary for swallowing these tablets and also suitable for Upper age group (geriatric), Lower age groups (paediatric) and patients who are in travelling.¹ These tablets have impulsive rapid breakdown in the mouth upon contact with saliva, dissolution of the active ingredient, and absorption through the buccal membrane while in contact.² Present day, diverse novel technologies which are modern had initiated to formulate Orodispersible tablets with fascinating features, like masking the bitterness ability, low breakdown time, pleasant feel at oral cavity and sugar free tablets for diabetic patients. The modern techniques applied in construction of Orodispersible



DOI: 10.5530/ijper.58.1s.17

Copyright Information :

Copyright Author (s) 2024 Distributed under Creative Commons CC-BY 4.0

Publishing Partner : EManuscript Tech. [www.emanuscript.in]

tablets are nanonization, sublimation, lyophilization, moulding, cotton candy process, direct compression, spray drying, mass extrusion, and quick dissolve film formation.³ The principles behind these techniques is to enhance porosity by inserting hydrophilic ingredients (excipients) in the tablets. The formulated trials derived from the above techniques differs from factors like taste, dissolution rate of the formulation in saliva, dosage form and drug stability, mechanical quality of product, overall bioavailability of drug and polymers and rate of absorption from saliva. By utilizing natural sweetening agents' concealment of the drug's taste was has proven to be a method for the formulation of various dosage forms that is both safety and efficacy. The development and characterization of an Orodispersible tablet of taste masked Nicardipine Hydrochloride are described in this paper. Nicardipine Hydrochloride is a calcium channel blocker which is commonly used to treat angina and high blood pressure. It is a bitter drug therefore masking the bitter taste is essential.⁴

Its formulation into a conventional dosage form may takes nearly 30 min to dissolve and absorb into systemic circulation. But taste masked Orodispersible tablet will give rapid action in reducing high blood pressure and also in angina conditions (a type of chest pain due to reduced blood flow to heart).⁵ Taste masking by natural sweetener Stevia i.e., extracted from *Stevia rebaudiana* plant was employed for masking the bitter taste. Since 2008, stevia glycoside was admitted to be safe and authorized in food products in the United States. It is a natural sweetener (herbal) that is 250-350 times sweeter than sucrose extracted from the *Stevia rebaudiana* plant. This will suitably mask the unpleasant taste of the drug so as to administer the drug as orally disintegrating tablets. For fast-dissolving tablets to be successful in the marketplace, unpleasant taste masking is an essential requirement. Various methods are also available for taste masking, which includes usage of ion exchange resins, microencapsulation, coacervation with gelation, complexing with artificial sweetener, and usage of monoglycerides. Nicardipine Hydrochloride is Dihydropyridines which is first generation have the same effects as Nifedipine. The drug has the advantage of increasing coronary sinus blood and myocardial contractility. It also shows a slight rise in rate of heart, cardiac output, and stroke volume with a decrease in systolic and diastolic measurements and systematic vascular resistance. The most important physicochemical property which effects the influence of its formulation and dissolution behaviour is solubility. Nicardipine hydrochloride is sparingly soluble in water. However, the solubility limitation can be overcome by using various solubility enhancing techniques like solid dispersion, cyclodextrin complexation, particle size reduction, salt formation, pH adjustment, co-solvents and surfactant etc to get rapid disintegration and dissolution. The selection of solubility enhancing techniques from the above various techniques depends on the dosage form it is intended to formulate. One can employ

alone or combination of these techniques to get the desired dissolution parameter to achieve.⁶

MATERIALS AND METHODS

Materials

Ingredients handled in the current research belong to specification samples. **Active Ingredient:** Nicardipine Hydrochloride (a gift sample from MANUS AKTTEVA BIOPHARMA LLP Pvt. Ltd., India).

Excipients: Lactopress Anhydrous 250 (Lactose anhydrous EP), OSMITROL (Mannitol Ph. Eur) VIVASOL (Croscarmellose Sodium Ph. Eur), Altalc (Talc Powder Ph. Eur) and Octadecanoate (Magnesium stearate Ph, Eur.,) were from S D Fine chemicals, Mumbai, India).

Unsheathing of Stevia Powder

Different steps involved in preparation of stevia powder is extraction from leaves, Purification, Filtration and Drying. First step in extraction and purification of stevia glycosides from leaves by immersing leaf litter with warm water, with stirring, and then liquid extract from the spent leaves are separated. Due to the over thickness of leaves it is frequently necessary to use a high water-to-leaf ratio, which results in a low concentration of steviol glycosides in the initial crude extract. with longitudinal helical agitator. The process is followed by clarification and drying in a microwave at 50°C. The dried powder is used in the formulations.

Analysis of Nicardipine Hydrochloride

The drug Nicardipine Hydrochloride alone was characterized as per different official compendial specifications and it was found to be yellow crystalline powder with odourless property. Practically it is having a melting point of 137°C, and Absorbance (λ_{max}) at 235 nm. Also, the purity of crude drug alone was 100.31%. All the evaluation results for the drug alone were found to matched with specifications.⁷

UV examination of Nicardipine Hydrochloride in 0.1 N hydrochloric

The known solution was prepared 1 $\mu\text{g/mL}$ of Nicardipine Hydrochloride in 0.1 N HCl medium were prepared and scanned over a ultraviolet range of 200-400 nm against blank solution (prepared by 0.1N HCl) in SHIMADZU Double beam UV Spectrophotometer. The absorbance values were found to show a peak at 235 nm which is similar to theoretical values.⁷

Construction of standard Calibration curves

To perform a standard curve (calibration curve) three different mediums are selected. Based on the solubility the medium selected are water, 0.1 N HCl, and synthetic human saliva.⁸

Construction of standard calibration curve by distilled water

Varied concentrations ranging from 2-50 µg/mL are prepared and absorbance is measured at 235 nm. The procedure for preparation includes 100 mg of drug dissolved in 100 mL of distilled water and further dilutions were prepared to get the drug concentrations ranging from 2-50 µg/mL from the above solution (stock). The absorbance was measured at double beam UV spectrophotometer and graph was plotted by taking drug concentration verses absorbance. The plot has shown linear graph.⁸

Construction of standard calibration curve in Synthetic human saliva (simulated salivary fluid)

As in the similar way of above process, the standard calibration curve was conducted by taking the simulated salivary fluid as medium and drug concentrations ranging from 2-50 µg/mL. The plot drawn by taking Absorbances on Y axis and Drug concentration on X axis had shown linear regression.⁸

Preparation of standard curve (calibration) in 0.1 N HCl

As in the similar way of above process, the standard calibration curve was conducted by taking the 0.1N HCl as medium and drug concentrations ranging from 2-50 µg/mL. The graph is plotted between Absorbances verses Drug Concentration had shown linear regression.⁹

Among all the above 0.1N HCl medium had shown linear graph with a regression equal to 1.

Preformulation study

The physical characteristics of Nicardipine Hydrochloride were examined to assess its organoleptic properties, including color, odour, and taste. The solubility of Nicardipine Hydrochloride was determined using a range of solvents such as water, acetone, chloroform, ethanol, methanol, DMSO, and Ethanol: Water (ratios). The melting point of Nicardipine Hydrochloride was measured using the Kshitij Innovations instrument, Model KI4070. The drug's hygroscopic properties were evaluated by exposing a sample to ambient room temperature and atmosphere, followed by moisture content analysis using LOD analysis. The flow behaviour of Nicardipine Hydrochloride was independently assessed using tests including the Angle of Repose, Carr's Index, and Hausner's Ratio. The purity of the drug was determined through titrimetric analysis, confirming it to be 100% pure. For formulation trials, solid dispersion techniques were employed for trials labelled F1 to F6, while tablets were prepared using the Direct Compression technique with varying concentrations of super disintegrants.

Formulation study Trials

Different formulation trials were taken to find optimized formula which meets the compendial specifications.¹⁰

Tablets Preparation

The formulation blend was compressed into round tablets by using 6mm punches and 28*17 mm dies. The tablets preparation was carried out after analysing the Drug (Nicardipine Hydrochloride), Stevia powder-Mixture of natural sweetener extract stevia with other excipients and drug for compatibility studies and other Preformulation evaluation studies then planned for compression of tablets.¹⁰ Formulation trials F1 to F6 were prepared using the solid dispersion technique and by Direct Compression technique tablets were prepared by using different concentrations of super disintegrants. The Formulation blend was evaluated for various preformulation tests including organoleptic properties, solubility, melting point, hygroscopicity, moisture content, purity of the drug, and flow properties, and compatibility study. The tablets were analysed for weight variation, hardness (3-4 kg/cm²) and friability (less than 1%). The disintegration time, content uniformity, water absorption ratio, wetting time and dissolution study for all the formulations were also studied.

'In vitro' characterization of drug content¹¹

The drug content of Nicardipine Hydrochloride was measured using the following formula:

$$\text{Drug content} = \frac{\text{Area of Sample} \times \text{Weight of standard} \times \text{Assay of standard} \times 0.7213 \times 110.33}{\text{Weight of sample}}$$

FTIR Spectrum

The compatibility study was carried out on drug (pure form) alone, Excipients alone, physical blend of drug and excipients mixture individually, and blend complex for FTIR study. The FTIR samples were analysed by using BRUKER ALPHA II analytical FTIR machine.¹²

Formulation of Orodispersable tablets

A total of six varied formulations were prepared and all the ingredients were passed through mess size 80 individually and collected. The ingredients were weighed and incorporated geometrically. Initially Anhydrous lactose, Mannitol, Crosscarmellose sodium, stevia and drug Nicardipine Hydrochloride was passed through sieves individually and they were blended after sieving. Then remaining part of the sweetening agent along with lubricating agent talc and Magnesium stearate were lubricated on the surface of the blend to impart sweetening property on the outer layer and by using lubricating agents to prevent compression issues.

Nicardipine Hydrochloride Orodispersable tablets were prepared as per the given Table 1.

Flow Property Evaluation of blend for Orodispersible tablet

Flow behaviour of the blend was estimated so as to reduce the flow of blend in commercial scale upon planning for Tech transfer to a commercial scale. The study is helpful to know the mixture of drug and excipients good flow properties. As the flow behaviour of the blend is directly proportional to evaluated properties like variation in weight of tablet, expected drug content.¹³

Angle of repose (°)

It is defined as the powder and horizontal plane's maximum angle surface of the pile.¹³

$$\theta = \tan^{-1} \frac{h}{r}$$

Where,

θ =angle of repose; h=height of the pile; r=radius.

Bulk density

The bulk density is calculated to know the weather the powers particles are packed loosely or heavily. Light powder particles have high packed volume where as vice versa for Heavy powder particle. The bulk density depended upon the distributed particle size. About 60 g powder is passed through a 60 No standard sieve. Approximately 20 g quantity weighed is added to a 100 mL graduated cylinder. The cylinder is mounted on the stable place and need to take the measurement up to the mark where the known mass of powder had occupied the volume. By using the formula need to calculate the bulk volume of the blend mixture.¹³

$$\text{Bulk density (P)} = \frac{\text{Mass of Powder}}{\text{Bulk volume}}$$

Tapped density

By using USP method II Tapped density was determined. The sample powder was passed through sieve No. 60 and 10 g of bend was top up to 100 mL graduated cylinder and it was placed at the top of tap density apparatus (Electrolab, ETD 1020). The tapped density tester was used to tap the cylinder 500 times at a rate of 250 drops per minute, and the initial volume (V_a) occupied by the blend was recorded. A further 750 taps were performed, and the volume was recorded. It was determined how much of a difference two tapping volumes are made. If there was a difference of more than 2%, then tapping was repeated again till it gets less than 2% noted as final tapped volume (V_b).¹³ The tapped density is calculated by using the following formulae;

$$\text{Tapped density} = \frac{\text{Weight of sample in (g)}}{\text{Tapped volume (Vb)}}$$

Compressibility (%)

The other name is Carr's Index. Compressibility is inversely linked to relative flow rate, particle size. Compressibility index is calculated by knowing the bulk density and tapped density values by using the following formulae.¹⁴

$$\text{Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

By using the above procedure calculation of t_d (Tapped density) and Bulk density is calculated and those values are incorporated into the Formulae of Carrs Index. So that the values obtained

Table 1: List of ingredients and Quantity (%) used for formulation.

Sl. No.	Ingredients	F ₁ (%)	F ₂ (%)	F ₃ (%)	F ₄ (%)	F ₅ (%)	F ₆ (%)
1	Nicardipine Hydrochloride	6.67	6.67	6.67	6.67	6.67	6.67
2	Lactose (Anhydrous)	40.00	39.11	38.33	37.78	37.22	36.67
3	Mannitol	40.00	39.11	38.33	37.78	37.22	36.67
4	Croscarmellose sodium	7.78	8.89	10	11.11	12.22	13.33
5	Stevia	3.33	4.00	4.44	4.44	4.44	4.44
6	Talc	1.11	1.11	1.11	1.11	1.11	1.11
7	Magnesium stearate	1.11	1.11	1.11	1.11	1.11	1.11
Total %		100	100	100	100	100	100

Table 2: Weight variation limits as per the pharmacopeial standards.

IP/BP	LIMITS	USP
80 mg OR less	±10%	0 or less
>80 mg and <250 mg	±7.5%	130 to 324 mg
More than 250 mg	±5%	More than 324 mg

after using the formulae lies in the flow range from Excellent to Very poor.

Hausner's Ratio

So as to find out the flow behaviour of blend by using Hausner's Ratio need to use the below mentioned formulae.¹⁵

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

By substituting the tapped density and Bulk density values in the above formula, a value in between 1.00-1.60 which shows the flow behaviour of the blend from Excellent to Very poor.

Tablet Evaluation/Characterization

Hardness

The Orodispersible Tablets are evaluated for Hardness, to determine whether the compressed tablets are having minimum Tensile strength to with stand the mechanical shocks that takes place during the shipping or handling the tablets. Plenty number of hardness testers are available which includes Monsanto, Pfizer, Strong Cobb, Erweka, Kraemer Elektronik, Portable Testers, Universal Testers, Rockwell etc. Among all the above available, Monsanto and Pfizer type of hardness testers are currently used widely. To maintain mechanical strength to Orodispersible tablets the range of hardness should lie in between 2-4 kg/cm².¹⁶ The hardness may impact the other evaluation properties like Disintegration, Dissolution which in turn shows its impact directly on Bioavailability.

Table 3: Flow Property Evaluation of Blend.

Sl. No.	Property	Formulations					
		F1	F2	F3	F4	F5	F6
1	Bulk Density (gm/cm ³)	0.25	0.23	0.24	0.24	0.24	0.24
2	Tapped Density (gm/cm ³)	0.23	0.21	0.22	0.22	0.22	0.22
3	Compressibility index (%)	8	8	8	8	8	8
4	Hausner's Ratio	1.08	1.09	1.09	1.09	1.09	1.09
5	Angle of Repose (°)	26	25	26	26	26	26
Flowability Result		Excellent Flow	Excellent Flow	Excellent Flow	Excellent Flow	Excellent Flow	Excellent Flow

Table 4: Preformulation study parameters and their results.

Sl. No.	Study Parameter	Results
1	Color	yellow, crystalline powder.
2	Odour	Odourless
3	Taste	slightly bitter taste.
4	Solubility (of Nicardipine Hydrochloride).	Soluble: Soluble in DMSO, Ethanol: water, methanol slightly soluble: Acetone, ethanol, chloroform and water.
5	Melting Point (°C)	145°C
6	Hygroscopicity	Non hygroscopic
7	Angle of Repose (°)	Poor flow
8	Compressibility Index (%)	Poor flow
9	Hausner's Ratio	Poor flow
10	Moisture content (%)	0.85%
11	Drug Purity (%)	100%

Weight variation

To ensure whether the compressed tablet is within the weight ranges or not as per the formulae are going to be evaluation by this parameter. As the weight varies from tablet then the amount of drug and excipients in the tablet varies which shows its impact directly on Dissolution, Drug Content and bioavailability. Generally, twenty tablets were typically selected at random from the batch and weighed. We calculate the average weight by taking sum of individual weights divided by 20. There shouldn't be the tablets with overweight or underweight. The tablets pass the USP test if there are no more than two tablets that are greater than the percentage limit or less than two times the percentage limit.¹⁷ To solve this problem the official compendial specifications are mentioned below in Table 2.

Friability

ROCHE friability apparatus is used to measure friability. As the study is conducted to determine the mechanical strength of the tablets during shipping, as the tablet packagings are handled roughly for transportation. By this evaluation we can determine whether the tablets are prone to chipping, cracking etc. 10 tablets are selected randomly and sum weight of ten tablets are taken as initial weight and subjected to the chambers of friabilator. After revolving for 4 min at 25 RPM, the tablets freed from the dust and weighed as Final weight.¹⁸ The friability is calculated by using.

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

The tablets after evaluating the friability should be less than 1% as per the official specification. If they are above 1% then the tablets are prone to chipping and cracking which are known as tableting defects.

Wetting time and water absorption ratio

The procedure for calculating wetting time is by taking 7 mL of water in a petri dish, add 2-4 drops of dye (phenolphthalein blue) and by keeping tissue paper folded on the top of water. Then a tablet is kept on the top of the tissue and the time taken for wetting of tablet is recorded. Through wicking action, water transports from petri dish to tissue paper and then to tablet the time is measured as wetting time.¹⁸ The wetted tablet was then measured. Water absorption ratio, R, was determined using the

$$R = [(W_a - W_b) - W_b] \times 100$$

Where, W_b = weight of tablet before water absorption, and W_a = weight of tablets after absorption.

Disintegration time

By using digital tablet disintegrating apparatus, disintegration time of each sample was recorded. The disaggregation process

was carried out at a temperature of $37 \pm 2^\circ\text{C}$, volume of 900 mL and medium of water.¹⁹

Content Uniformity

Two tablets were taken and powder them finely then the powder is added to a 100 mL volumetric flask containing 6.8 phosphate buffer, sonicate it for 15 min. Allow the insoluble particles to settle to bottom, then filter the contents. Take out 10 mL from the above filtrate and diluted the remaining quantity with 6.8 phosphate buffer. Again, it is sonicated for 10 min and left undisturbed for 5 min.²⁰ Then the above sample is analysed spectrophotometrically at 235 nm.

The content uniformity is calculated by using the formula as follows.

$$(\text{TC/D}) (\text{AU/AS}).$$

T=labelled quantity (mg), of Nicardipine Hydrochloride in the tablet,

C=Concentration, (mg per mL) Nicardipine Hydrochloride.

D=concentration, (mg/ mL Nicardipine Hydrochloride in the solution from the tablet, based on the labelled quantity per tablet and the extent of dilution and AU and AS are the absorbances of the solution from sample and standard solution respectively.

In vitro dissolution

The *in vitro* dissolution studies were carried out using USP apparatus type II at 50 rpm. The dissolution medium used was 0.1 N Hydrochloric acid (900 mL volume) which is maintained at $37 \pm 0.5^\circ\text{C}$. Aliquots of dissolution media were withdrawn at different time intervals and amount of Nicardipine Hydrochloride was measured by determining absorbance at 235 nm.²¹ The dissolution experiments were conducted in triplicate. Not less than 80% (Q) of the labelled amount of drug Nicardipine Hydrochloride is dissolved in 5 min.

Stability study

RESULTS

Pre-formulation studies

The organoleptic properties were examined physically by choosing different volunteers to determine colour, odour and taste of crude drug Nicardipine Hydrochloride. The results of colour, odour, taste are yellow, crystalline powder, Odourless, slightly bitter taste respectively. The solubility of the drug is also conducted by taking different solvents like water, acetone, chloroform, ethanol, methanol, DMSO, and ethanol: water (ratios). And the solubility in different solvents are shown in the below Table 3. Nicardipine Hydrochloride had shown high solubility in DMSO, Ethanol: Water, and methanol. The melting point was determined by using the instrument Kshiti Innovations, Model KI4070 and it

had shown a result of 145°C. The hygroscopic study was done by putting a drug sample in a petri dish and exposing the drug to room temperature and atmosphere, and analysed for moisture content by LOD analysis, where it had shown result of non-hygroscopic (no uptake of moisture from atmosphere). Flow behaviour of drug alone (Nicardipine Hydrochloride) was conducted and study of Angle of Repose, Carr's Index, Hausner's Ratio had shown Poor behavioural flow. The purity of the drug is also conducted by titrimetric analysis and it was found to be 100% pure with a moisture content of 0.85% in pure drug. The results of all these parameters were disclosed in the Table 4.

FTIR Spectrum

The FTIR Spectrum study indicates clearly that there was no incompatibility among the blend mixture used for preparing the Orodispersible tablets. The FTIR spectrum reveals several peaks

at specific wavenumbers, providing insights into the functional groups and molecular vibrations present in the sample. At 1704 cm^{-1} , the peak suggests the presence of a carbonyl group ($\text{C}=\text{O}$), commonly found in aldehydes, ketones, and carboxylic acids. The peak at 1646 cm^{-1} indicates the presence of an amide group ($\text{C}=\text{O}$) typically found in proteins or peptide backbones. A peak at 1620 cm^{-1} suggests the presence of aromatic rings, indicating the presence of benzene or other aromatic compounds. The peak at 1533 cm^{-1} can be attributed to $\text{C}=\text{C}$ stretching vibrations in conjugated double bonds, commonly found in aromatic compounds. The peak at 1492 cm^{-1} may be related to $\text{C}-\text{H}$ bending vibrations in alkanes or aliphatic compounds. The presence of methyl ($-\text{CH}_3$) or methylene ($-\text{CH}_2-$) groups can be inferred from the peak observed at 1457 cm^{-1} . At 1353 cm^{-1} , the peak could be associated with $\text{C}-\text{N}$ stretching vibrations, indicating the presence of an amine group. The peak at 1309 cm^{-1}

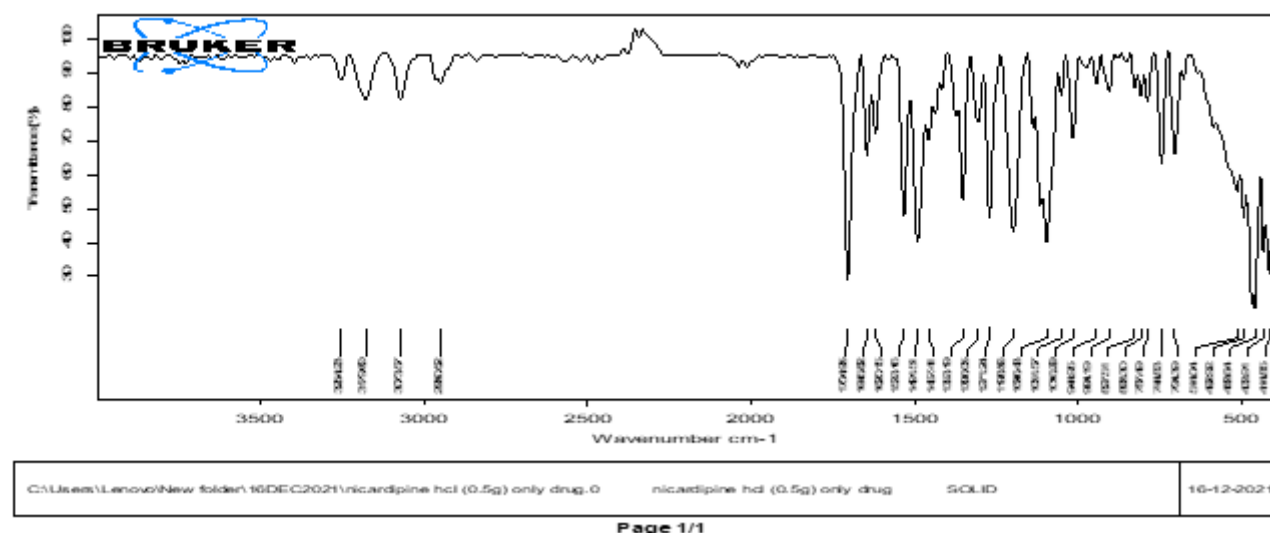


Figure 1A: FTIR spectrum of Nicardipine Hydrochloride Alone.

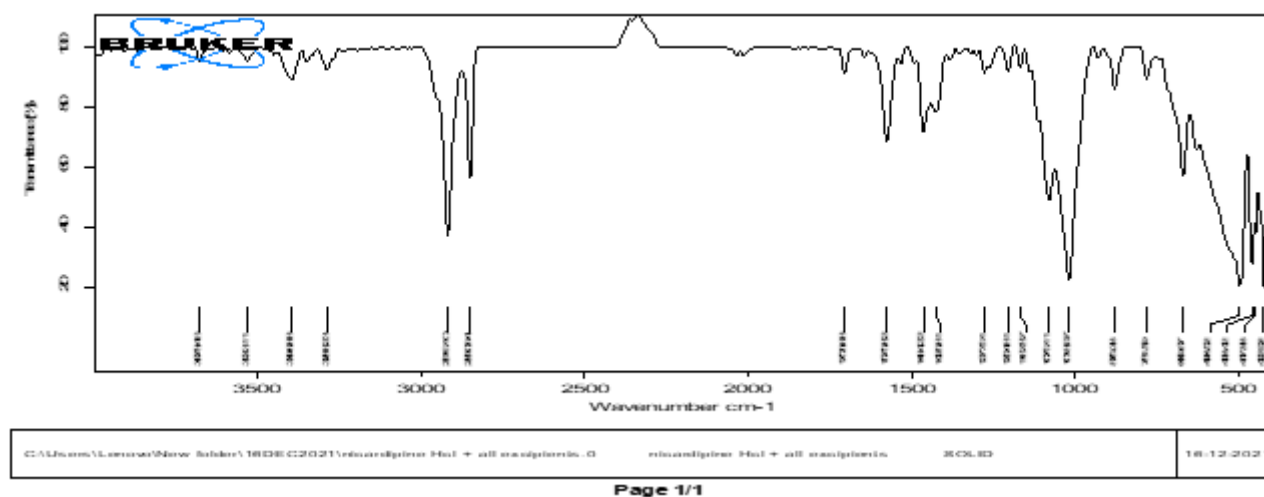


Figure 1B: FTIR spectrum of Nicardipine Hydrochloride and Stevia.

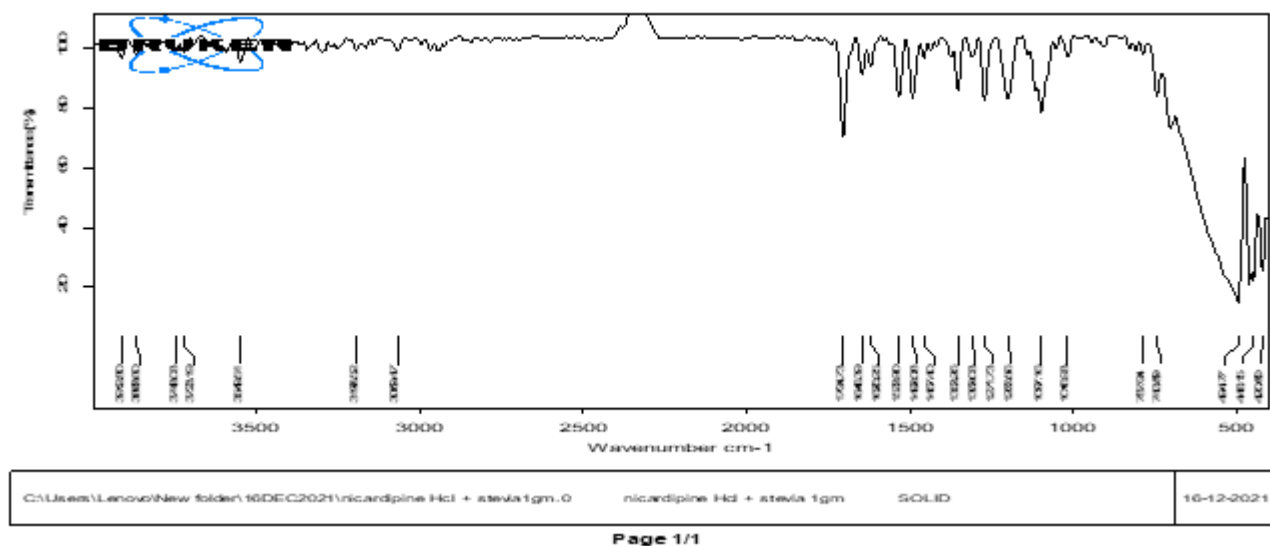


Figure 1C: FTIR spectrum of Drug and All Excipients (Blend Mixture).

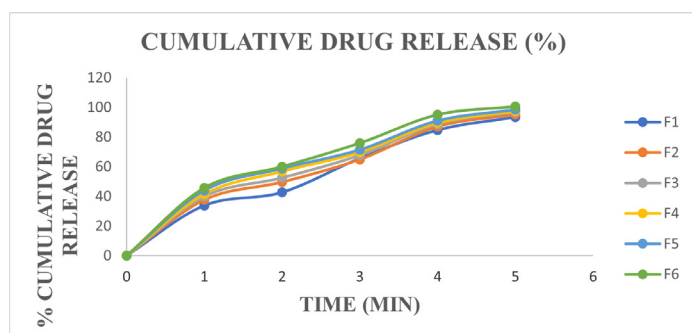


Figure 2: Dissolution study of different formulations.

is commonly observed in polysaccharides or carbohydrates and can be attributed to C-O stretching vibrations. The presence of C-O stretching vibrations in ethers or esters can be suggested by the peak at 1271 cm^{-1} . The peak at 1200 cm^{-1} is often associated with C-N stretching vibrations in primary amines or secondary amides. At 1097 cm^{-1} , the peak may be related to C-O stretching vibrations in alcohols or phenols. The presence of C-N stretching vibrations in secondary amines can be indicated by the peak observed at 1016 cm^{-1} . The peak at 787 cm^{-1} may suggest the presence of a disubstituted benzene ring. The peak at 743 cm^{-1} can be attributed to C-H bending vibrations in substituted aromatic compounds. The peak at 494 cm^{-1} is often associated with out-of-plane bending vibrations of aromatic compounds. The presence of C-Cl stretching vibrations in alkyl chlorides can be suggested by the peak observed at 448 cm^{-1} . Finally, the peak at 420 cm^{-1} is often associated with metal-ligand vibrations or metal-oxygen stretching vibrations. From the FTIR it is evident that there are no chemical interactions between drug and excipients (Figure 1A, 1B, 1C).

Flow Property Evaluation of blend for Orodispersible tablet: Powdered blend was evaluated for Compress ability Index,



Figure 3: First order plot between LOG % Unreleased vs Time.

Hausners Ratio and Angle of Repose and the evaluation results are tabulated in Table 3.

Evaluation of tablets and its Results

After compressing the blend mixture to an Orodispersible tablets, they were characterized for different specifications like Hardness, Weight Variation, Friability, Wetting Time, Disintegration Time, Drug content, Dissolution. The results were shown in Table 5.

Dissolution studies

Cumulative % Drug release results were tabulated in Table 6. The comparative dissolution profile results are shown as Figure 2 and First Order plot was shown at Figure 3.

Stability study

The results and the comparative dissolution graph were shown in Table 7 and Figure 4.

DISCUSSION

The successful passing of the compatibility study, as determined by FTIR analysis, confirms that the components of the formulation blend are compatible with each other. This is a crucial aspect in ensuring the stability and effectiveness of the final product. The

Table 5: Evaluation of Orodispersible Tablets.

Formulations							
Sl. No.	Evaluation parameter	F1	F2	F3	F4	F5	F6
1	Weight Variation (mg)	100±4	100±4	100±4	100±4	100±4	100±4
2	Hardness (Kg/cm ²)	4.15±0.68	4.05±0.55	3.82±0.45	3.78±0.56	3.85±0.35	3.50±0.58
3	Friability (%)	0.81±0.01	0.79±0.02	0.76±0.02	0.75±0.01	0.75±0.02	0.73±0.01
4	Disintegration Time (Sec)	76.55±0.66	70.85±0.81	69.16±0.45	65.24±0.58	56.75±0.35	51.46±0.66
5	Wetting Time (Sec)	10.45±1.15	10.47±1.21	10.45±1.24	10.46±1.21	10.45±1.19	10.46±1.21
6	Water Absorption ratio (%)	96.56±0.60	97.45±0.41	98.86±0.22	98.36±0.75	98.68±0.86	98.89±0.55
7	Content Uniformity (%)	98.20±0.25	98.70±0.42	99.10±0.84	99.40±0.75	99.30±0.33	99.50±0.48

Table 6: Dissolution Study of Formulations.

Cumulative % Drug release in Formulations							
Time (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	
0	0	0	0	0	0	0	
1	33.79±2.78	37.63±4.55	39.89±3.35	41.54±1.27	43.95±2.45	45.69±3.55	
2	42.67±4.68	49.62±3.25	52.53±2.52	56.87±3.65	58.84±2.79	59.97±3.45	
3	65.57±6.87	64.86±4.88	67.78±5.75	69.85±4.59	71.54±3.58	75.83±3.16	
4	84.66±5.81	86.98±5.10	88.81±2.65	89.68±4.21	91.09±3.98	94.96±1.48	
5	93.38±1.55	95.24±1.10	96.89±1.35	97.56±1.19	98.59±0.68	100.5±1.56	

Table 7: Stability Data for 40°C and 75% RH.

Sl. No.	Evaluation	1 Month	2 Month	3 Month
1	Hardness (kg/cm ²)	3.45±0.55	3.45±0.55	3.45±0.55
2	Disintegration Time (sec)	49.66±0.66	51.66±0.46	52.66±0.35
3	Content Uniformity (%)	97.80±0.26	98.30±0.38	97.20±0.20
4	Cumulative % Drug Release (at 5 Min)	99.85±1.16	98.55±1.66	97.85±1.35

preformulation studies conducted were aimed at formulating the product in a stable manner, taking into consideration factors such as solubility, melting point, hygroscopicity, moisture content, and flow properties. By conducting these studies, the formulation can be optimized to enhance its stability and overall quality.

The utilization of the solid dispersion method demonstrated notable advantages in terms of disintegration and dissolution. Solid dispersion is a technique used to enhance the solubility and dissolution rate of poorly water-soluble drugs by dispersing them in a hydrophilic carrier. The results obtained from the dissolution tests indicated that the optimized F6 tablets achieved satisfactory

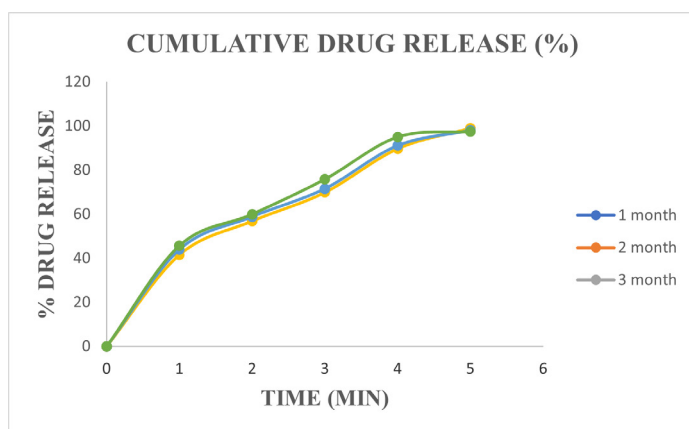


Figure 4: Dissolution profile at 40°C and 75% RH for tablets stored from 1-3 months.

dissolution within 5 min. This indicates that the drug is released effectively from the formulation, facilitating its absorption and potential therapeutic efficacy.

The evaluation tests performed on the tablets met the specifications outlined in the pharmacopeial standards. The tablets exhibited desirable characteristics such as weight variation within acceptable limits, appropriate hardness, and friability below the specified threshold. These results affirm the compliance of the tablets with quality standards and provide confidence in their performance. Additionally, the taste of the tablets after being blending with the natural sweetener stevia was found to be favourable. This indicates that the incorporation of stevia, a commonly used sugar substitute, can enhance the palatability of the tablets, potentially improving patient acceptance and compliance.

The stability study conducted over the course of 3 months under accelerated conditions demonstrated that the optimized F6 tablets maintained their integrity and performance. This indicates that the formulation remains stable over an extended period, suggesting it has the potential for commercial-scale production. Based on these comprehensive results, it can be concluded that the formulation is stable, meets the desired quality specifications, and exhibits satisfactory dissolution characteristics. This paves the way for further development and potential commercialization of the formulation, offering promising prospects for its successful introduction into the market.

CONCLUSION

As Nicardipine Hydrochloride drug when given through oral route (conventional dosage form) the bioavailability of the drug is less. So, the drug is formulated through Orodispersible tablet so as to bypass the first pass metabolism and to enhance the bioavailability. As the Nicardipine Hydrochloride belongs to BCS Class II drug the solubility of the drug is enhanced by solid dispersion technique. As the drug is also having bitter taste, to overcome this natural sweetener stevia powder is extracted

from *Stevia rebaudiana* plant. Organoleptic characteristics like appearance, odour and taste are essential factors in assessing the consumer acceptability, thereby the commercial success in the market. Thus, taste masking of oral pharmaceuticals has become a potential tool to improve patient compliance and commercial success of the product. Palatability is enhanced as it belongs to natural sweetener. Also, the compatibility between stevia and drug, followed by stevia along with other excipients are analysed with FTIR studies and the results were found to be compatible with each other. A total six formulations were prepared by direct compression technique and croscarmellose sodium as super disintegrant to meet the disintegration time less than 70 sec. By the end due to use of solid dispersion technique the solubility of drug is enhanced as it can be observed through dissolution results. The accelerated stability study (For 3 Months) also showed better evaluation results. The entire study shows an urged need for novel development through taste masked Orodispersible tablets. The present study also shows an advantage to patient compliance as it shows immediate therapeutic effect than marketed conventional dosage form (capsule).

ACKNOWLEDGEMENT

I hereby acknowledge to my parents and all my teachers who made me stand in a position to teach many students. We gratefully acknowledge the Aditya Pharmacy College, affiliated to JNTU Kakinada for providing research facilities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

FTIR: Fourier transforms infrared; **UV:** ultraviolet; **USP:** United States Pharmacopoeia; **HDPE:** High Density Polyethylene; **RH:** Relative Humidity; **BCS:** Biological Classification System.

SUMMARY

The study investigated the development of an Orodispersible tablet formulation of Nicardipine Hydrochloride to enhance its bioavailability and improve patient compliance. The solubility of the drug was enhanced by using a solid dispersion technique and the bitter taste was masked using stevia powder, a natural sweetener. The compatibility between stevia and the drug was analyzed through FTIR studies and was found to be compatible. The Orodispersible tablets were prepared using direct compression and croscarmellose sodium as a super disintegrant. The study results showed improved solubility and disintegration time. The accelerated stability study for 3 months also showed favorable results. The study highlights the importance of developing novel Orodispersible tablet formulations to improve patient compliance and commercial success.

REFERENCES

- Shahi SR, Agrawal GR, Shinde NV, Shaikh SA, Shaikh SS, Somani VG, *et al.* Formulation and *in vitro* evaluation of orodispersible tablets of etoricoxib with emphasis on comparative functionality evaluation of three classes of superdisintegrants. *Rasayan J Chem.* 2008;1(2):292-300.
- Zaki RM, Alfadhel M, DevanathaDesikan Seshadri V, Albagami F, Alrobaian M, Tawati SM, *et al.* Fabrication and characterization of orodispersible films loaded with solid dispersion to enhance rosvastatin calcium bioavailability. *Saudi Pharm J.* 2023;31(1):135-46. doi: 10.1016/j.jsps.2022.11.012, PMID 36685296.
- Abed KK, Hussein AA, Ghareeb MM, Abdulrasool AA. Formulation and optimization of orodispersible tablets of diazepam. *AAPS PharmSciTech.* 2010;11(1):356-61. doi: 10.1208/s12249-010-9387-y, PMID 20232267.
- Pabari RM, Ramtoola Z. Effect of a disintegration mechanism on wetting, water absorption, and disintegration time of orodispersible tablets. *J Young Pharm.* 2012;4(3):157-63. doi: 10.4103/0975-1483.100021, PMID 23112534.
- Segale L, Maggi L, Ochoa Machiste EO, Conti S, Conte U, Grenier A, *et al.* Formulation design and development to produce orodispersible tablets by direct compression. *J Drug Deliv Sci Technol.* 2007;17(3):199-203. doi: 10.1016/S1773-2247(07)50036-5.
- Daravath B, Naveen C, Vemula SK, Tadikonda RR. Solubility and dissolution enhancement of flurbiprofen by solid dispersion using hydrophilic carriers. *Braz J Pharm Sci.* 2018;53(4). doi: 10.1590/s2175-97902017000400010.
- Salawi AJP. An insight into preparatory methods and characterization of orodispersible film-a review. *Pharmaceutics (Basel).* 2022;15(7):844. doi: 10.3390/ph15070844, PMID 35890143.
- Elsayed MMA, Aboelez MO, Elsadek BEM, Sarhan HA, Khaled KA, Belal A, *et al.* Tolmetin sodium fast dissolving tablets for rheumatoid arthritis treatment: preparation and optimization using Box-Behnken design and response surface methodology. *Pharmaceutics.* 2022 Apr 18;14(4):880. doi: 10.3390/pharmaceutics14040880, PMID 35456714.
- Heinig R, Weimann B, Dietrich H, Böttcher MF. Pharmacokinetics of a new orodispersible tablet formulation of vardenafil: results of three clinical trials. *Clin Drug Investig.* 2011;31(1):27-41. doi: 10.2165/11584950-000000000-00000, PMID 20925442.
- Ibrahim HK, El-Setouhy DA. Valsartan orodispersible tablets: formulation, *in vitro*/*in vivo* characterization. *AAPS PharmSciTech.* 2010;11(1):189-96. doi: 10.1208/s12249-009-9354-7, PMID 20112137.
- Pabari RM, Ramtoola Z. Application of face centred central composite design to optimise compression force and tablet diameter for the formulation of mechanically strong and fast disintegrating orodispersible tablets. *Int J Pharm.* 2012;430(1-2):18-25. doi: 10.1016/j.ijpharm.2012.03.021, PMID 22465631.
- Vlad RA, Antonoaea P, Todoran N, Rédei EM, Birsan M, Muntean DL, *et al.* Development and evaluation of cannabidiol orodispersible tablets using a 23-factorial design. *Pharmaceutics.* 2022;14(7):1467. doi: 10.3390/pharmaceutics14071467, PMID 35890362.
- Kokott M, Klinken S, Breitzkreutz J, Wiedey R. Downstream processing of amorphous solid dispersions into Orodispersible tablets. *Int J Pharm.* 2023;631:122493. doi: 10.1016/j.ijpharm.2022.122493, PMID 36528189.
- Radicioni M, Connolly S, Stroppolo F, Granata G, Loprete L, Leuratti C. Bioequivalence study of a novel orodispersible tablet of meloxicam in a porous matrix after single-dose administration in healthy volunteers. *Int J Clin Pharmacol Ther.* 2013;51(3):234-43. doi: 10.5414/CP201781, PMID 23380429.
- Maqbool A, Aamir MN, Naeem M. Formulation and evaluation of fast dissolving films embedded with nanoparticles of mirtazapine hydrochloride. *JCP.* 2022;6(1):6-18. doi: 10.56770/jcp2022612.
- Ockun MA, Baranauskaite J, Uner B, Kan Y, Kirmizibekmez H. Preparation, characterization and evaluation of liposomal-freeze dried anthocyanin-enriched Vaccinium Arctostaphylos L. fruit extract incorporated into fast dissolving oral films. *J Drug Deliv Sci Technol.* 2022;72:103428. doi: 10.1016/j.jddst.2022.103428.
- Chintamaneni PK, Nagasen D, Babu KC, Mourya A, Madan J, Srinivasarao DA, *et al.* Engineered upconversion nanocarriers for synergistic breast cancer imaging and therapy: current state of art. *J Control Release.* 2022;352:652-72. doi: 10.1016/j.jconrel.2022.10.056, PMID 36328078.
- Shaik EB, Pindiprolu SKSS, Phanikumar CS, Samuel T, Kumar BVN, Santhoshi PM, *et al.* Optical emissions of chitosan modified LaAlO₃: Bi³⁺, Tb³⁺ nanoparticles for bio labeling and drug delivery to breast cancer cells. *Opt Mater.* 2020;107:110162. doi: 10.1016/j.optmat.2020.110162.
- Puttewar TY, Kshirsagar MD, Chandewar AV, Chikhale RV. Formulation and evaluation of orodispersible tablet of taste masked doxylamine succinate using ion exchange resin. *J King Saud Univ Sci.* 2010;22(4):229-40. doi: 10.1016/j.jksus.2010.05.003.
- Pindiprolu SKSS, Kumar CSP, Kumar Golla VS, P L, K SC, S K EB, *et al.* Pulmonary delivery of nanostructured lipid carriers for effective repurposing of salinomycin as an antiviral agent. *Med Hypotheses.* 2020;143:109858. doi: 10.1016/j.mehy.2020.109858, PMID 32516655.
- Puttewar TY, Kshirsagar MD, Chandewar AV, Chikhale RV. Formulation and evaluation of orodispersible tablet of taste masked doxylamine succinate using ion exchange resin. *J King Saud Univ Sci.* 2010;22(4):229-40. doi: 10.1016/j.jksus.2010.05.003.
- Sheikh FA, Aamir MN, Haseeb MT, Ajmal Shah M, Farid-Ul-Haq M, Alqarni M, *et al.* Appraisal of the pharmacokinetic profile, histopathology, and stability studies of a fast-dissolving oral film based on natural polysaccharide. *Pak J Pharm Sci.* 2022; 35(3(Special)):937-44. PMID 35791591.

Cite this article: Dasari N, Kumar CSP, Gummadi RK, Pindiprolu SSSK, Balla S, Masa A, *et al.* Application of Novel Natural Sweetening Agent-Stevia in Formulation, Evaluation of Nicardipine Hydrochloride Orodispersible for Rapid Absorption. *Indian J of Pharmaceutical Education and Research.* 2024;58(1s):s176-s186.