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DEVELOPMENT AND IN VITRO EVALUATION OF A FLOATING DRUG DELIVERY SYSTEM OF NICORANDIL

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ABSTRACT

The present study focused on the formulation and evaluation of gastro-retentive floating tablets of Nicorandil designed to provide controlled drug release over a period of 24 hours. The tablets were prepared by direct compression using natural polymers such as almond gum and guar gum to achieve sustained release and floating characteristics. Among all the formulations, batch F5 containing almond gum showed superior performance and was selected as the optimized formulation based on its buoyancy, swelling behavior, drug release profile, and kinetic analysis. The drug release from F5 followed zero-order and Higuchi models, while also fitting well with the Korsmeyer–Peppas equation. Overall, the developed floating tablets enhanced gastric retention, which may contribute to improved bioavailability of Nicorandil.

INTRODUCTION

Pharmacotherapy refers to the use of drugs to achieve safe and effective therapeutic outcomes by maintaining appropriate drug concentrations in blood or tissues without causing toxicity. The objectives of pharmacotherapy vary depending on the disease condition and available treatment options [1]. These include preventive therapy to avoid disease occurrence, symptomatic therapy to relieve clinical symptoms, abortive therapy to halt disease progression, and curative therapy to eliminate the underlying cause.

For successful treatment, it is essential that the drug reaches the site of action quickly and maintains its therapeutic concentration for an adequate duration while minimizing adverse effects. This requires careful selection of dosage form, dose, and dosing schedule to ensure optimal drug delivery and patient safety. The formulation should be designed in such a way that it provides consistent drug levels despite physiological variations within the body.

Among various routes, oral administration is the most preferred due to its convenience, cost-effectiveness, and high patient compliance. A large proportion of marketed drug products are oral dosage forms, particularly tablets. These can be designed in multiple forms such as conventional tablets, chewable tablets, buccal tablets, or controlled release systems depending on therapeutic needs.

An ideal dosage regimen should ensure rapid attainment of therapeutic levels at the target site and maintain these levels for the required duration of treatment. Different therapeutic approaches are applied based on clinical requirements. Preventive therapy aims to avoid complications such as hypertension-related disorders or gout symptoms using antihypertensives and urate-lowering agents. Symptomatic therapy focuses on relieving symptoms, as

seen in allergy management using antihistamines or in multiple sclerosis with corticosteroids. Abortive therapy is used to reduce the severity and duration of conditions like migraine through serotonin receptor agonists. Curative therapy involves eliminating the root cause of diseases, such as using antibiotics to treat sinus infections [2].

In the present investigation, Nicorandil was selected as the model drug for the development of gastro-retentive floating tablets using the direct compression technique. Nicorandil is widely used in the management of cardiovascular conditions such as hypertension and angina pectoris, which require consistent therapeutic levels. Due to its short half-life (approximately 1.33 hours), the drug needs to be administered multiple times a day (2-4 doses) to maintain effective plasma concentration. This frequent dosing may lead to poor patient compliance and increased chances of missed doses.

To overcome these limitations, a controlled release formulation capable of delivering the drug over an extended period, preferably once daily, is desirable. Gastro-retentive floating drug delivery systems offer an effective approach by prolonging gastric residence time and delaying gastric emptying, thereby enhancing drug release and therapeutic action. Hydrophilic and swellable polymers are commonly employed in such systems to achieve sustained drug release [3].

The present study was designed to evaluate the influence of different polymers on extending drug release up to 24 hours.

OBJECTIVES OF THE STUDY

- To assess the compatibility between the drug and selected excipients
- To prepare a calibration curve of Nicorandil using 0.1 N HCl
- To evaluate pre-compression parameters of the powder blend suitable for direct compression
- To analyze post-compression characteristics of the prepared tablets
- To formulate floating tablets using natural polymers such as almond gum and polymeric materials like cetostearyl alcohol
- To study and compare dissolution profiles to determine the drug release kinetics and mechanism

METHOD AND METHODOLOGY [4-7]

Pre-formulation Studies

Pre-formulation studies involve the systematic evaluation of the physical and chemical characteristics of a drug substance, both alone and in combination with excipients. It represents the initial phase in the logical development of a dosage form. The primary aim is to gather essential information required to design a stable, safe, and bioavailable formulation. These studies enhance the likelihood of developing an effective and acceptable pharmaceutical product.

For successful formulation, it is important to assess the physicochemical properties of the drug, including appearance, solubility, bulk density, tapped density, compressibility index, angle of repose, and melting point.

Objectives of Pre-formulation Studies

Pre-formulation evaluation of the active pharmaceutical ingredient (API), excipients, and their mixtures is carried out to:

- Establish specifications for the API
- Examine compatibility between drug and excipients
- Characterize the reference product

Pre-formulation studies are broadly classified into:

a) API characterization

b) Drug–excipient compatibility studies

API Characterization

Organoleptic Properties

Characteristics such as color, odor, and taste of the drug are noted using descriptive terms.

Solubility

A measured quantity of drug is added to a solvent, and its solubility is determined based on standard classification ranges.

Table 1: Solubility Classification

Description	Volume of solvent (mL per gram of solute)
Very soluble	< 1
Freely soluble	1 – 10
Soluble	10 – 30
Sparingly soluble	30 – 100
Slightly soluble	100 – 1000
Very slightly soluble	1000 – 10,000
Practically insoluble	> 10,000

Density Studies

Bulk Density (Db) Bulk density is defined as the ratio of the mass of powder to its bulk volume. It is determined by transferring a known quantity of powder into a graduated cylinder and measuring its volume.

Formula:

$Db = M / Vb$

Where:

M = mass of powder

Vb = bulk volume

Tapped Density (Dt)

Tapped density is the ratio of the mass of powder to its volume after mechanical tapping until a constant volume is obtained.

Formula:

$Dt = M / Vt$

Where:

M = mass of powder

Vt = tapped volume

Compressibility Index (Carr's Index)

Carr's Index indicates the flow properties of powder and is expressed as a percentage.

Formula:

$I = [(Dt – Db) / Dt] \times 100$

Table 2: Carr's Index Classification

Carr's Index (%)	Flow Property
5 – 15	Excellent
12 – 18	Good
18 – 23	Fair to passable
23 – 35	Poor
35 – 38	Very poor
> 40	Extremely poor

Angle of Repose (θ)

The angle of repose is used to evaluate the flow behavior of powders. It is defined as the maximum angle formed between the surface of a powder heap and the horizontal plane.

Formula:

$\tan \theta = h / r$

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

Where:

h = height of the powder heap

r = radius of the base

The powder is allowed to flow through a funnel to form a cone, and the height and radius are measured to calculate the angle.

Table 3: Angle of Repose Classification

Angle (degrees)	Flow Property
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

FT-IR Spectral Studies

Infrared spectra of the pure drug and formulation excipients were recorded using a Jasco FT-IR spectrophotometer by employing the KBr pellet method in a ratio of 1:100. The spectra were obtained in the transmittance mode over a wavenumber range of 400–4000 cm^{-1} with a resolution of 4 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Thermal analysis was performed using a DSC Q200 instrument (TA Instruments, NJ, USA) equipped with a refrigerated cooling system and modulation capability. The DSC chamber was purged with dry nitrogen at a flow rate of 50 ml/min, while the cooling system operated at 150 ml/min. Calibration of the instrument was carried out using empty aluminum pans for baseline correction and standard materials such as cyclohexane, indium, and tin for temperature accuracy. Approximately 3–5 mg of the sample was sealed in aluminum pans and heated from an initial temperature to above its melting point under a nitrogen atmosphere. The obtained thermograms were analyzed using Universal Analysis Software.

Analytical Method for Estimation of Nicorandil

UV Spectrophotometric Method

A UV spectrophotometric method was employed for the estimation of Nicorandil by measuring absorbance at 262 nm using 0.1 N HCl as the solvent medium.

Preparation of Standard Stock Solution

An accurately weighed quantity (100 mg) of Nicorandil was dissolved in 0.1 N HCl and the volume was adjusted to 100 ml in a volumetric flask to obtain a stock solution of 1000 µg/ml.

Procedure

The stock solution was further diluted with 0.1 N HCl to prepare a series of concentrations ranging from 10 to 50 µg/ml. The absorbance of these solutions was recorded at 262 nm using a double-beam UV spectrophotometer, with 0.1 N HCl as the blank. The method's reproducibility was confirmed by analyzing six independent samples of Nicorandil.

Formulation of Controlled Release Floating Tablets of Nicorandil

Preparation of Core Tablets

Controlled release floating tablets of Nicorandil were prepared by the direct compression method. The drug was blended with varying concentrations of natural polymers such as guar gum and almond gum. The mixture was passed through a #60 mesh sieve to ensure uniform particle size. Sodium bicarbonate was incorporated as a gas-generating agent and mixed thoroughly for about 10 minutes. Cetostearyl alcohol was then added to the blend, followed by the addition of talc and magnesium stearate, which were also sieved through #60 mesh. The final blend was mixed for an additional 5 minutes and compressed into tablets using an 8 mm punch on a rotary tablet press.

Table 4: Formulation of Nicorandil Controlled Release Floating Tablets

Ingredients mg/tab	Formulation					
	F1	F2	F3	F4	F5	F6
Nicorandil	30	30	30	30	30	30
Guar gum	20	40	60	-	-	-
Almond gum	-	-	-	20	40	60
Sodium bi carbonate	40	40	40	40	40	40
Ceto sterile alcohol	50	50	50	50	50	50
Lactose	150	130	110	150	130	110
Talc	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5
Total weight (mg)	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg

Evaluation of Cilnidipine Fast Dissolving Tablets

Physical Appearance

The tablets were visually examined to assess their general appearance, including size, shape, color, odor, taste, surface texture, and presence of any identifying marks.

Weight Variation Test

Twenty tablets from each formulation were individually weighed using an electronic balance, and the average weight was calculated. The percentage deviation was determined using the following formula:

% Weight Variation = [(Average weight − Individual weight) / Average weight] × 100

Pharmacopoeial Limits:

Table 5: British Pharmacopoeia (BP):

Average Weight (mg)	Maximum Deviation (%)
< 130	5
130–324	7.5
> 324	10

Table 6: Indian Pharmacopoeia (IP):

Average Weight (mg)	Permissible Deviation (%)
≤ 130	10
130–324	7.5
> 324	5

Thickness

The thickness of tablets was measured using a vernier caliper. Five tablets from each batch were evaluated, and the average value was recorded.

Hardness

Tablet hardness was determined using a Monsanto hardness tester. Five tablets from each batch were tested, and the mean hardness was calculated in kg/cm².

Friability

Friability was evaluated using a Roche friabilator. Ten tablets were initially weighed (W_1) and rotated at 25 rpm for 100 revolutions. After dedusting, the tablets were reweighed (W_2). The percentage friability was calculated as:

% Friability = [($W_1 - W_2$) / W_1] × 100

Drug Content Estimation

Nicorandil controlled release floating tablets were randomly selected from each batch and finely powdered. A weighed quantity of the powder equivalent to the required dose was transferred into a 100 ml volumetric flask, and about 70 ml of 0.1 N HCl was added. The mixture was shaken intermittently for 30 minutes to ensure complete extraction of the drug, and the volume was adjusted to 100 ml with distilled water. A 10 ml aliquot of this solution was centrifuged, and the clear supernatant was filtered using a Millipore filter. The filtrate was appropriately diluted, and absorbance was measured at 262 nm using a UV spectrophotometer. The analysis was performed in triplicate (or ten times, N=10) for each batch to ensure accuracy.

In-vitro Dissolution Studies

Dissolution testing was carried out using a USP Type II (paddle) dissolution apparatus at a rotation speed of 100 rpm. The dissolution medium consisted of 900 ml of 0.1 N HCl, maintained at a temperature of 37 ± 0.5°C. Samples (5 ml) were withdrawn at predetermined intervals over a period of 24 hours and replaced with an equal volume of fresh medium to maintain constant volume. The samples were filtered, and the amount of drug released was quantified by measuring absorbance at 262 nm using a UV spectrophotometer.

Drug Release Kinetics (Curve Fitting Analysis)

The in vitro drug release data of the optimized formulation were analyzed using various kinetic models to understand the release mechanism. The models applied include:

- **Zero-order model:** Cumulative percentage drug release versus time
- **First-order model:** Log percentage drug remaining versus time
- **Higuchi model:** Cumulative drug release versus square root of time
- **Korsmeyer–Peppas model:** Log drug release versus log time

The release kinetics was evaluated by plotting the dissolution data according to these models to determine the order and mechanism of drug release.

RESULTS

Pre-formulation Parameters

The pre-formulation characteristics of Nicorandil were evaluated to assess its suitability for tablet formulation. The obtained values indicate acceptable flow and compression properties.

Table 7: Pre-formulation Parameters

S.No	Parameter	Observation
1	Drug	Nicorandil (API)
2	Angle of Repose	25.12°
3	Bulk Density	0.601 g/cc
4	Tapped Density	0.596 g/cc
5	Compressibility Index	19.14%
6	Hausner's Ratio	1.425
7	Melting Point	92–93°C

Drug–Excipient Compatibility Studies

Compatibility studies were performed to evaluate the interaction between Nicorandil and various excipients under accelerated and ambient storage conditions. No visible changes were observed after one month, indicating good compatibility.

Table 7: Physical Compatibility Results

Material Combination	Observation (After 1 Month)
Nicorandil + Guar gum	No change
Nicorandil + Almond gum	No change
Nicorandil + Sodium bicarbonate	No change
Nicorandil + Cetostearyl alcohol	No change
Nicorandil + Lactose	No change
Nicorandil + Talc	No change
Nicorandil + Magnesium stearate	No change

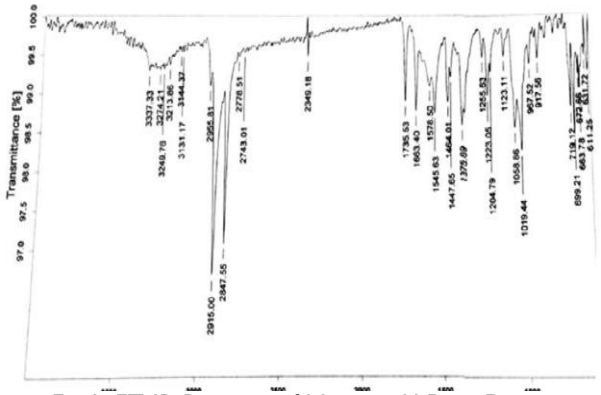

Fig 1: FT-IR Reports of Nicorandil Pure Drug

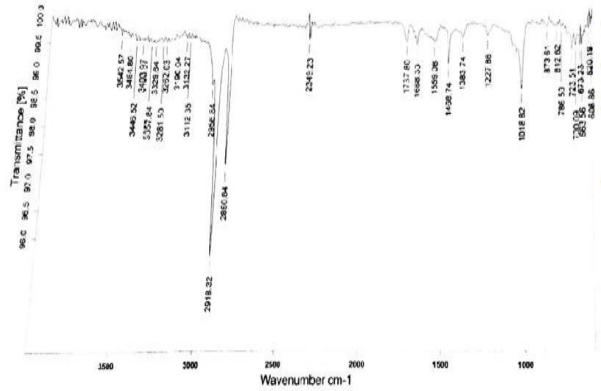

Fig 2: FT-IR Reports of optimized formula

Differential scanning calorimetry

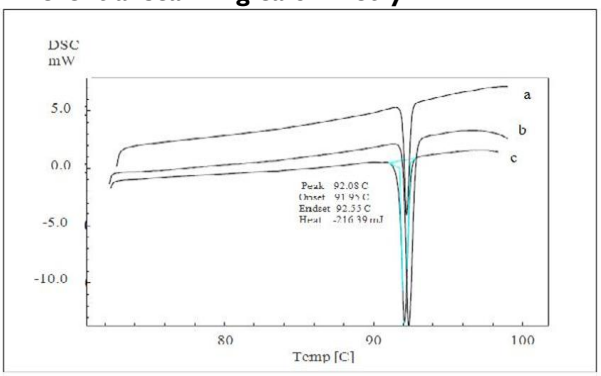

Fig 3: DSC Thermogram of optimized formulation

Analytical Method for Estimation of Nicorandil by U.V Spectrophotometry.

Table 8: Standard Calibration Data of Nicorandil in 0.1 N HCL

Concentration (µg/ml)	Absorbance (nm)
0	0
10 (µg/ml)	0.110
20 (µg/ml)	0.194
30 (µg/ml)	0.291
40 (µg/ml)	0.391
50 (µg/ml)	0.512

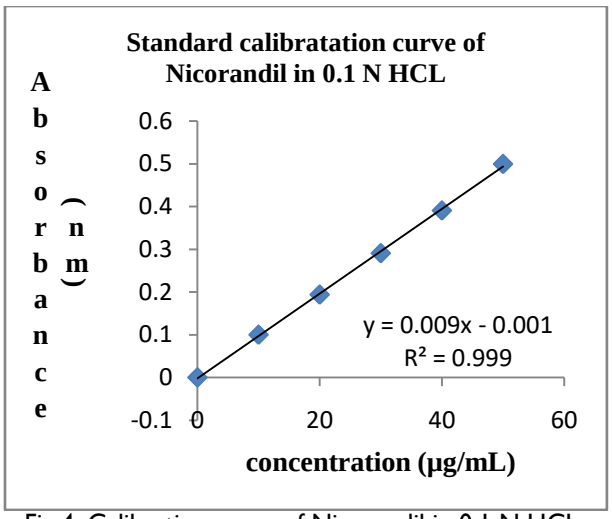

Fig 4: Calibration curve of Nicorandil in 0.1 N HCL buffer.

Table 9: Standard Calibration Curve for the Nicorandil in pH 7.4 phosphate buffer

S. No	Concentration (µg/ml)	Absorbance(nm)
1	0	0
2	10(µg/ml)	0.084
3	20 (µg/ml)	0.195
4	30 (µg/ml)	0.278
5	40 (µg/ml)	0.384
6	50 (µg/ml)	0.499

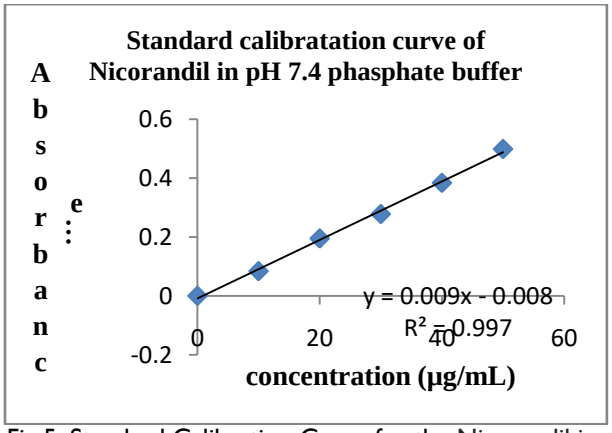

Fig 5: Standard Calibration Curve for the Nicorandil in pH 7.4 phosphate buffer

Pre – compression parameters:

Table 10: Micromeritic properties of the granules of Nicorandil formulation

Formulation code	Bulk density (g/	Tapped density (g/	Hausner's ratio	Angle of repose(θ)	Compressibility Index (%)
F1	0.610	0.645	1.19	24.04	19.20
F2	0.613	0.654	1.14	25.19	18.10
F3	0.599	0.632	1.15	25.18	20.17

F4	0.609	0.648	1.32	25.22	22.42
F5	0.611	0.651	1.41	25.21	20.21
F6	0.610	0.661	1.28	23.15	22.12

Post – compression parameters

Table No: 11Post compression parameters NicorandilControlled Release floating Tablets

Formulation code	Weight Variation (mg)	Hardness (kg/cm²)	% Friability (% loss)	Buoyancy time	Floating lag time	Drug content
F1	299 ± 2.0	6.5 ± 0.2	0.20	4.0	12.50	101.3 ± 0.2
F2	295 ± 2.0	6.6 ± 0.3	0.16	4.1	10.41	99.1 ± 0.3
F3	305 ± 2.0	6.1 ± 0.3	0.18	4.2	09.31	103.4 ± 0.2
F4	299± 2.0	6.3 ± 0.3	0.19	4.8	08.00	101.1 ± 0.3
F5	300 ± 2.0	6.4 ± 0.3	0.17	4.9	08.44	104.3 ± 0.2
F6	301 ± 3.0	6.2 ± 0.3	0.15	4.2	09.00	101.1 ± 0.3

***In-vitro* dissolution studies**

Table 12: Dissolution studies for Nicorandil Controlled Release floating Tablets.

Dissolution with 01N 900ml, RPM 100, λ max 262 nm							
% Cumulative Drug Release							
S.NO	Time (hrs)	F1	F2	F3	F4	F5	F6
1.	0	0	0	0	0	0	0
2.	1	15.36	10.26	18.63	12.36	16.35	11.23
3.	2	25.36	21.56	32.65	25.63	26.59	24.36
4	4	36.89	31.21	48.63	38.96	38.96	39.56
5	6	49.85	42.32	56.98	48.63	49.56	48.25
6	8	58.6	56.36	69.58	58.65	58.63	59.63
7	10	69.48	69.32	76.82	69.35	62.38	65.23
8	12	75.36	76.35	80.56	71.69	79.56	78.59
9	16	81.56	85.63	85.26	89.65	85.63	86.35
10	20	89.26	91.25	91.26	91.63	91.56	96.48
11	24	91.23	95.63	98.23	96.23	97.86	99.59

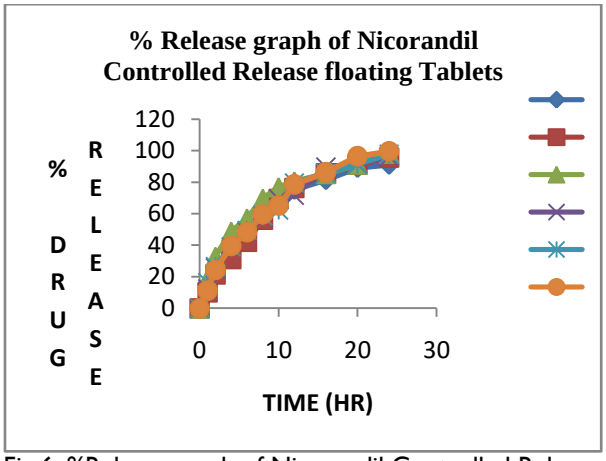

Fig 6: %Release graph of Nicorandil Controlled Release floating Tablets with guar gum and almond gum (F1-F6).

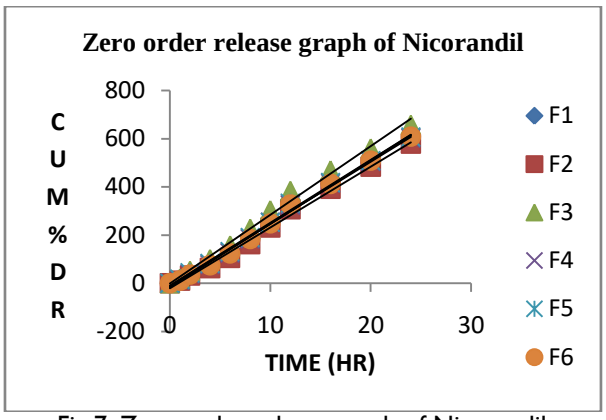

Fig 7: Zero order release graph of Nicorandil Controlled Release floating Tablets with guar gum and almond gum (F1-F6).

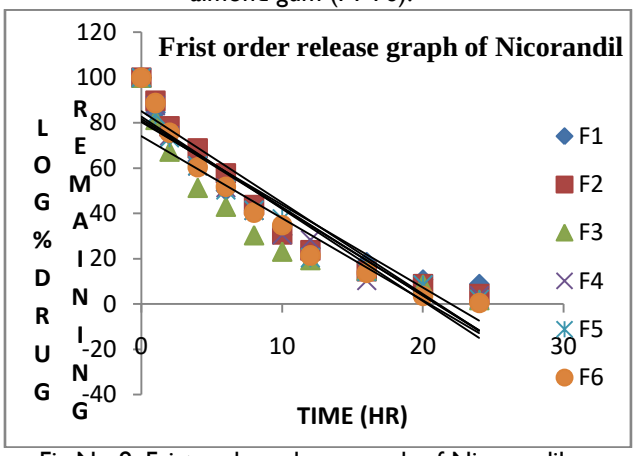

Fig No 8: Frist order release graph of Nicorandil Controlled Release floating Tablets with guar gum and almond gum (F1-F6).

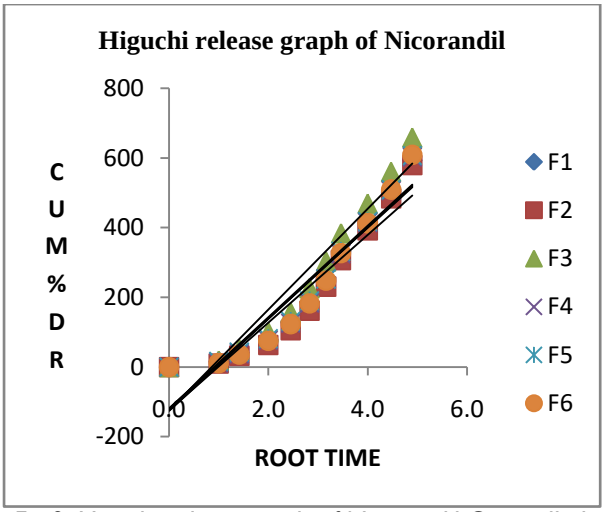

Fig 9: Higuchi release graph of Nicorandil Controlled Release floating Tablets with guar gum and almond gum (F1-F6).

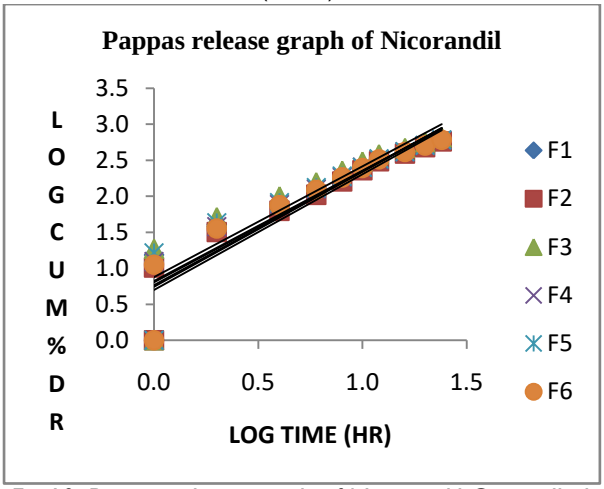

Fig 10: Pappas release graph of Nicorandil Controlled Release floating Tablets with guar gum and almond gum (F1-F6).

Table 13: Dissolution kinetics of Nicorandil Controlled Release floating Tablets with guar gum and almond gum (F1-F6).

Correlation co-efficient				
Formulation	**Zero order**	**First order**	**Higuchi**	**Pappas**
F1	0.994	0.873	0.913	0.853
F2	0.993	0.905	0.894	0.892
F3	0.993	0.824	0.927	0.830
F4	0.996	0.895	0.908	0.871
F5	0.996	0.902	0.912	0.847
F6	0.996	0.909	0.904	0.880

DISCUSSION

Pre-formulation Studies

Identification of Nicorandil

The preliminary identification tests confirmed the characteristics of Nicorandil. The drug was found to be slightly soluble in water and methanol, which is consistent with reported data.

Angle of Repose

The measured angle of repose (25.12°) indicated good flow properties of the powder, making it suitable for tablet formulation by direct compression.

Density Studies

The bulk density and tapped density of Nicorandil were found to be 0.601 g/cc and 0.596 g/cc, respectively. These values suggest acceptable packing ability and flow behavior.

Compressibility Index and Hausner's Ratio

The compressibility index (19.14%) and Hausner's ratio (1.42) indicated fair to good flow characteristics of the drug powder, which are suitable for further processing.

FT-IR Studies

The FT-IR spectra of the pure drug and its formulations showed characteristic peaks without significant shifts or disappearance. This confirms the absence of chemical interaction between Nicorandil and the selected excipients such as guar gum and almond gum.

Differential Scanning Calorimetry (DSC)

DSC analysis indicated that the drug remained stable in the presence of excipients. The thermograms suggested possible dispersion of the drug within the polymer matrix, indicating good compatibility and stability.

Analytical Method

Nicorandil was quantified using a UV spectrophotometric method. The absorbance at 262 nm confirmed the suitability and reliability of the method for drug estimation.

Preparation of Floating Tablets

Controlled release floating tablets of Nicorandil were successfully prepared using the direct compression technique. The drug was blended with varying concentrations of guar gum and almond gum, followed by the addition of sodium bicarbonate as a gas-generating agent. Cetostearyl alcohol, talc, and magnesium stearate were incorporated to improve tablet properties. The final blend was compressed into tablets using an 8 mm punch.

Evaluation of Post-compression Parameters

All formulations complied with Indian Pharmacopoeia (IP) standards.

Weight Variation: The average tablet weight ranged from 295 ± 2 mg to 305 ± 3 mg, within acceptable limits.

Hardness: Tablet hardness ranged from 6.1 to 6.6 kg/cm², indicating adequate mechanical strength.

Friability: The friability values (0.15–0.20%) were below 1%, confirming good durability.

Drug Content: The drug content ranged from 99.1% to 104.3%, indicating uniform drug distribution.

In-vitro Dissolution Studies

Dissolution studies were conducted using USP Type II apparatus in 0.1 N HCl (900 ml) at 37 ± 0.5°C. Drug release was monitored up to 24 hours. All formulations (F1–F6) showed sustained drug release depending on polymer concentration.

1. F1: 91.23%
2. F2: 95.03%
3. F3: 98.23%
4. F4: 96.23%
5. F5: 97.86%
6. F6: 99.59%

Among these, formulation F6 exhibited the highest drug release (99.59%) over 24 hours and was considered the optimized formulation, particularly due to the use of almond gum.

Curve-Fitting Analysis

The drug release data were fitted into various kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The optimized formulation F6 showed the highest correlation coefficient (r = 0.996) for the zero-order model, indicating a constant drug release rate. The release mechanism was best described by the Higuchi model (r = 0.904), suggesting diffusion-controlled release. The results also indicated anomalous (non-Fickian) diffusion, implying that drug release occurs through a combination of diffusion and polymer relaxation mechanisms.

SUMMARY & CONCLUSION

Nicorandil floating tablets were developed using direct compression with guar and almond gums for sustained release. The optimized formulation (F6) showed 99.59% release over 24 hours, following zero-order and diffusion mechanisms. Results confirmed good compatibility, buoyancy, and controlled release, demonstrating the effectiveness of natural polymers in gastro-retentive drug delivery.

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CONFLICT OF INTEREST

Not declared

INFORMED CONSENT AND ETHICAL STATEMENT

Not applicable

AUTHOR CONTRIBUTIONS

Both are contributed equally.

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