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Formulation and Evaluation of Gastro-Retentive Floating Tablets of Nicorandil

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ABSTRACT

The present study to formulate and evaluation of gastro-retentive floating tablets of Nicorandil to retard the drug release in a controlled release manner for 24 hrs. The formulations were prepared by using natural gums like almond gum and guar gum to prepare control release floating dosage forms by direct compression method. The % of drug release of Nicorandil was compared with all the formulations, F5 is the best with almond gum was selected as optimized formulation based on buoyancy behavior, swelling behavior, drug release data, and kinetic study. The order and mechanism of drug release of F5 were identified as zero-order and Higuchi mechanism, whereas the drug release behavior was best fitted to the Korsmeyer-Peppas model. The controlled release floating tablets of Nicorandil using the combination of almond gum was successfully formulated as an approach to increase gastric residence time and thereby improving its bioavailability.

INTRODUCTION:

Controlled Release Drug Therapy:

For many decades treatment of acute diseases or chronic illnesses has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, suppositories, creams, ointments, liquids, aerosols, and injectables. Present nova a day's these controlled release dosage forms most use full technology for the improve the release rate.

Gastro retentive systems are made to design and develop drug delivery systems that can remain in the stomach for a prolonged period and can provide therapeutically effective plasma drug concentration for a longer period by releasing the drug in a controlled and reproducible manner, thus reducing the side effects, dosing frequency and minimizing the fluctuation in plasma drug concentration. Gastro retentive systems significantly prolong the gastric retention time of drugs which increases bioavailability and decreases drug waste. Drug targeting to the stomach and upper small intestine is also possible. These systems are also important for drugs that are degraded in the intestine or drugs for which absorption is needed locally in the stomach like antacids and certain enzymes. These systems can also be used for drugs having selective absorption in the stomach e.g. Albuterol.

Gastro retentive drug delivery systems are needed for the drugs which exhibit low solubility and poor absorption due to inconstant gastrointestinal transit. These systems are also suitable for drugs that degrade at alkaline pH and which require local or sustained delivery to the stomach or upper gastric region to treat certain specific disorders.

Nicorandil was a common choice of drug in cardiovascular diseases like hypertension and angina pectoris, which require constant monitoring. It has a short steady-state half-life (1.33 hr) and necessitating the administration 2 to 4 times daily to maintain adequate plasma levels of the drug. Therefore, patients were directed to adhere to a strict routine medication several times a day and there may be a chance of missing a dose. In such case, the formulation releasing the drug in a controlled manner for a prolonged period (preferably once daily) will aid the patient's convenience way by avoiding the need to take the dosage form 2 to 4 times daily. Controlled release gastro retentive dosage form was one of the choices and most feasible approaches which were capable of controlling the rate of drug delivery, sustaining

the duration of therapeutic activity, and/or targeting the delivery of drug to tissue by prolonging the gastric retention time (GRT) and delay the gastric emptying time (GET).

MATERIALS AND METHODS:

Nicorandil (Torrent Pharmaceuticals (P) Ltd. Gujarat), Guar gum (Coloreon Asia Pvt. Ltd, Mumbai), Almond gum (Chemiloids, Vijayawada), Cetostearyl alcohol (Chemiloids, Vijayawada) Sodium bicarbonate (S.D. Fine-Chem. limited, Mumbai), Lactose (S.D. Fine-Chem. limited, Mumbai), Talc (SReidel (India) Chemicals, Hapur), and Magnesium stearate (S.D. Fine-Chem. limited, Mumbai).

METHODS:

Pre-formulation studies:

Bulk Density (Db):

It is the ratio of the mass of powder to the bulk volume of powder. It was measured by pouring the weight powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$Db = M/Vb$$

Where M = mass of powder. Vb = bulk volume of the powder.

Tapped density (Dt):

It is the ratio of the total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by

$$Dt = M/Vt$$

Where M = mass of powder. V_t = tapped volume of the powder.

Carr's Index (I):

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

$$I = Dt-Db/Dt*100$$

Where D_t = tapped density of the powder. D_b = bulk density of the powder.

The angle of Repose (θ):

The friction forces in loose powder can be measured by the angle of repose θ. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

$$Tan\theta = h/r$$

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

Where θ = the angle of repose, h = the height, r is the radius.

The powder mixture was allowed to flow through the funnel fixed to a stand at a definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

FT-IR Spectral studies:

The IR spectra for the formulation excipients and pure drugs were recorded on Jasco FT-Infrared spectrophotometer using the KBr palette technique (1:100) at their solution rate of 4 cm^{-1}. Spectrum was integrated into transmittance mode at the wavenumber range 400-4000 cm^{-1}utions were.

Differential scanning calorimetry:

Conventional DSC and MTDSC experiments were performed using DSC Q200 (TA Instruments, NJ, USA) with a refrigerated cooling assembly (RCS) and a modulated capability. The DSC cell was purged with 50 ml/min dry nitrogen, and the RCS was purged with 150 ml/min nitrogen. The DSC cell was calibrated for baseline using empty pans of matched weight and for temperature using three temperature standards (cyclohexane, T_m = 279.54° K; indium, T_m = 429.61° K; tin T_m = 504.93° K). About 3-5 mg of samples were exposed to the desired heating rates from the desired starting temperature to above the melting point of Nicorandilunder dry nitrogen purging (50 ml/min) in hermetically sealed aluminum pans. The data was analyzed using Universal Analysis Software from TA Instruments.

Analytical method for estimation of Nicorandil:

U. V. Spectrophotometer:

A Spectrophotometric method based on the measurement of absorbance at 262 nm in 0.1 N HCl buffer was used in the present study for estimation of Nicorandil.

Preparation of standard stock solution of Nicorandil:

100 mg of Nicorandil was accurately weighed and dissolved in 0.1N HCl buffer in a 100 ml volumetric flask and the solution was made up to volume with the same media to get the 1000 µg/ml stock solution as standard.

Method

The standard solution of Nicorandil was subsequently diluted with 0.1 N HCl buffer to obtain series of dilutions containing 10, 20, 30, 40, 50 µg of Nicorandil per 1ml of solution. The absorbance of the above solutions was measured in Elico double beam UV spectrophotometer at 262 nm using 0.1 N HCl buffer as blank. The reproducibility of the method was tested by analyzing six separately weighed samples of Nicorandil.

Formulation of Nicorandil Controlled Release floating tablets:

The controlled release floating tablets of Nicorandil were prepared by direct compression technique. Nicorandil was mixed with guar gum and almond gum in different concentrations in different formulations. After passing this mixture through the #60 mesh sieve, a floating agent such as sodium bicarbonate was added in geometric dilution and mixing continued for an additional 10 min. To this mixture, Cetostearyl alcohol was added. After that talc and magnesium stearate each passed through the #60 mesh sieve were added and mixing continued for an additional 5 min. The blend was then compressed into tablets using 8 MM station mini-press.

Table No. 1: 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	300	300	300	300	300

Evaluation of Nicorandil Controlled Release Floating Tablets:

Physical appearance:

The physical appearance of tablets is determined by visual identity which involves the measurement of several factors such as tablet size, shape, colour, odour, taste, surface texture, and any identification marks present on the tablet.

Weight variation test:

The weight variation test is performed by taking 20 tablets from each formulation and weighing the individual tablets by using an electronic balance. Their average weight was calculated as:

$$\% \text{ Weight variation} = (WA - WI) \times 100 / WI$$

Where,

WI = Individual weight of the tablets

WA = Average weight of the tablet

Table No. 2: Weight variation specifications (B.P)

The average weight of the tablet (mg)	Maximum difference allowed
Less than 130	5
130-324	7.5
More than 324	10

Table No. 3: Weight variation specifications (I.P)

The average weight of tablet (mg)	Percentage deviation
130 or less	10
130 to 324	7.5
More than 324	5

Hardness (kg/cm^2):

The hardness of the tablets was tested using a Monsanto hardness tester. Five tablets from each batch were tested for hardness.

% Friability:

The Friability of the tablets was determined in a Roche friabilator. Ten tablets were weighed initially (w_1) and placed in the friabilator that revolves at a speed of 25 RPM, dropping those tablets at a distance of six inches height with each revolution and rotated in the friabilator for 100 revolutions. After completion of rotations, the tablets were dedusted and weighed (w_2). The percent loss in weight or friability (f) is calculated by using the formula.

% Friability= (Initial weight- Final weight)/ Initial weight × 100

% Drug content:

Nicorandil Controlled Release Floating Tablets from a batch were taken at random and was crushed to a fine powder. The powdered material was transferred into a 100 ml volumetric flask and 70 ml 0.1N HCl buffer was added to it. It was shaken occasionally for about 30 minutes and the volume was made up to 100 ml by adding distilled water. About 10 ml of the solution from the volumetric flask was taken and centrifuged. The supernatant solution from the centrifuge tube was collected and again filtered by using a Millipore filter. Then the

filtrate was subsequently diluted and the absorbance was measured at 262 nm. This test was repeated ten times (N = 10) for each batch of tablets. The amounts of Nicorandil estimated from different batches were depicted.

***In-vitro* dissolution studies:**

In-vitro dissolution study was performed by using USP type II dissolution test apparatus (paddle type) [Lab, India (DS-8000, Mumbai)] at 100 RPM. 900ml of 0.1N HCl buffer was used as the dissolution medium which was maintained at 37 ± 0.5ºC. Aliquots of dissolution medium (5mL) were withdrawn up to 24 hr at regular intervals and replaced with equal volume to maintain the constant volume of dissolution medium and were filtered. The amount of drug dissolved was determined by a UV spectrophotometer by measuring the absorbance of the sample at 262 nm.

RESULTS AND DISCUSSION:

Formulations of Nicorandil control release floating tablets are prepared by using natural gums like Guar gum and Almond gum was impact on *In- Vitro* dissolution rate.

Pre-formulation studies:

The Active pharmaceutical ingredient (Nicorandil) and excipients were blended and evaluated for different parameters as clarified before. Bulk density was found in the limit of 0.599 - 0.613 g/cm^3 and the tapped density between 0.632-0.661 g/cm^3. By using both density data Carr's compressibility was determined. The compressibility record was found between 18.10 - 22.42 % and the Hausner's ratio was found to be 1.14 -1.41. The result shows good flow properties of the blend. The good flow properties of powder were also evident from the angle of repose that ranges from 23.15^0 - 25.22^0. In the present examination, all powder mixes indicated excellent flow properties. The outcomes have appeared in Table No. 4.

Precompression parameters:

Table No. 4: Micromeritic properties of the granules of Nicorandil formulation

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Angle of repose(ɵ)	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

FT-IR Spectral studies:

FT-IR studies:

From the FT-IR spectra, it was concluded that similar characteristic peaks with a minor difference for the drug and the FT-IR formulation. Hence, it appears that there was no chemical interaction between the drugs and excipients used**.** The IR Spectra of with, Guar gum, Almond gum shown. The following peaks were observed in as well as Nicorandil with excipients.

FT-IR Reports of Nicorandil

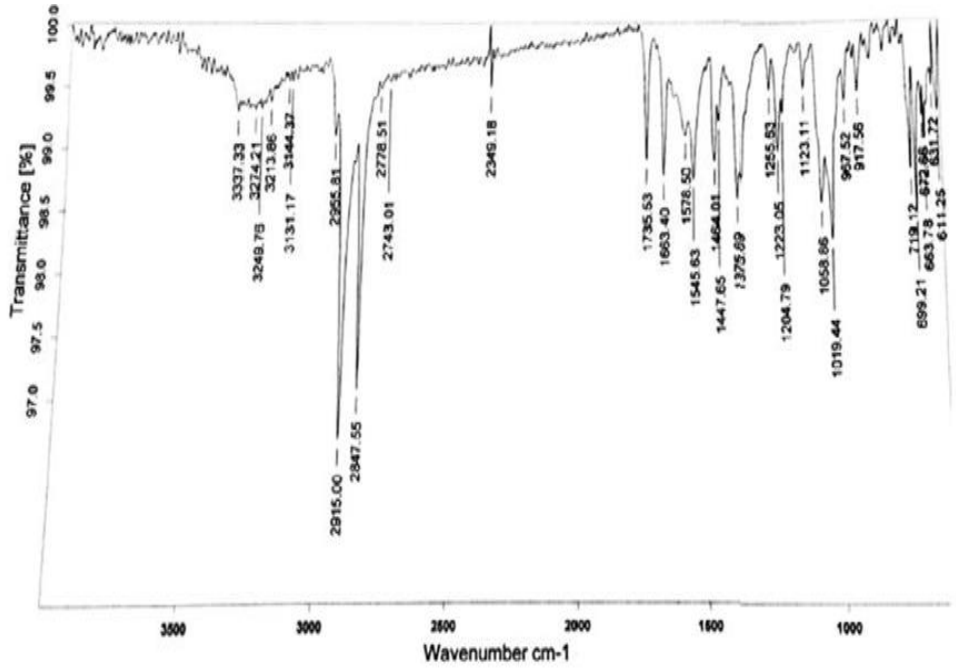

Figure No. 1: FT-IR Reports of Nicorandil

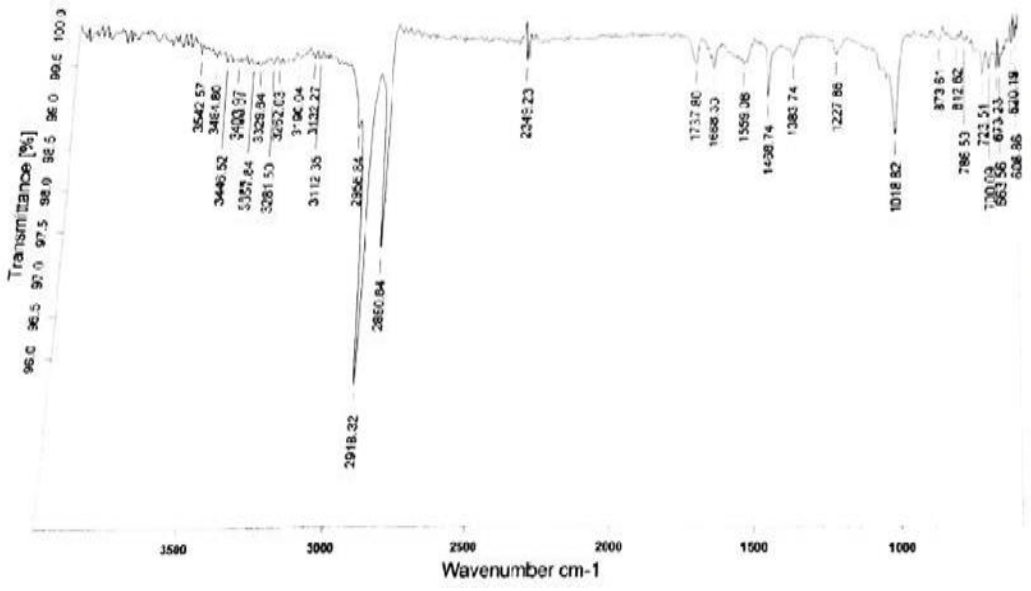

Figure No. 2: FT-IR Reports for Nicorandil Optimized formula.

Differential scanning calorimetry:

DSC indicated better drug stability in presence of natural gums. A stronger drug amorphization and entrapment in natural gums were observed.

Differential scanning calorimetry:

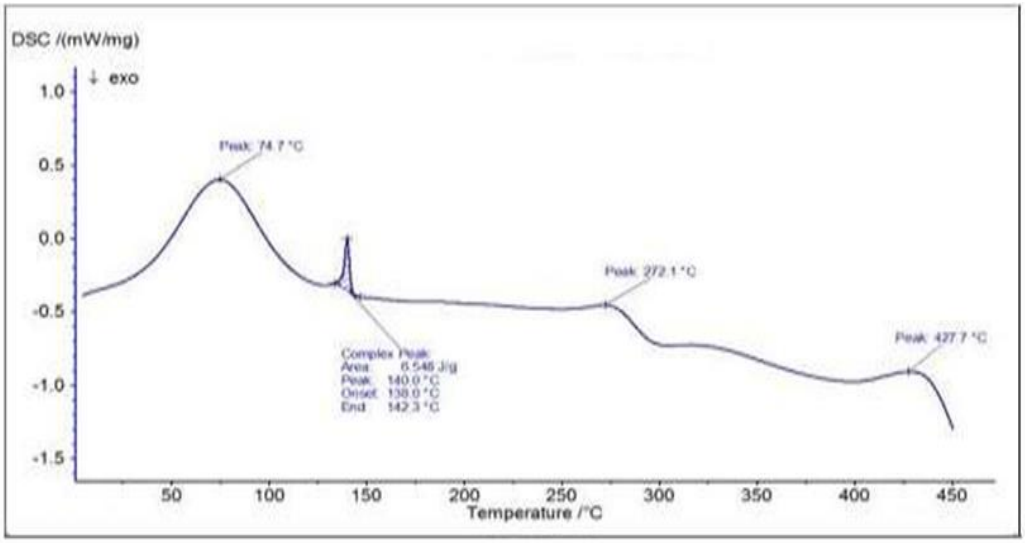

Figure No. 3: DSC Thermogram for Nicorandil.

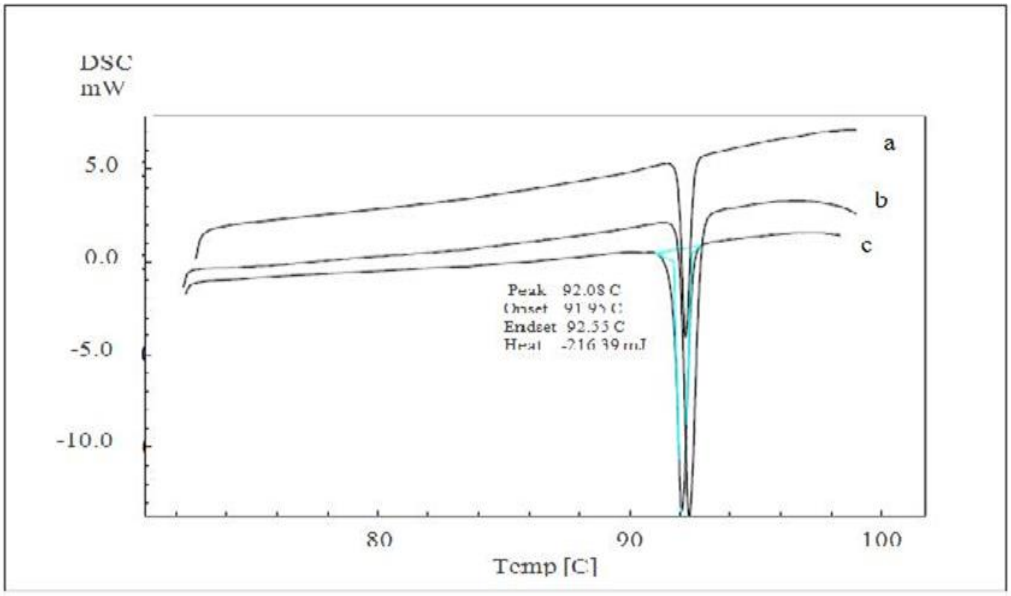

Figure No. 4: DSC Thermogram of optimized formulation

Analytical method development:

Nicorandil was estimation using UV/VIS spectrophotometer method. It was found that under UV/VIS spectrophotometer standard absorbance of the peak of Nicorandil was 0.291 µg/ml,

Table No. 5: Standard Calibration Data of Nicorandil in 0.1 N HCl

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

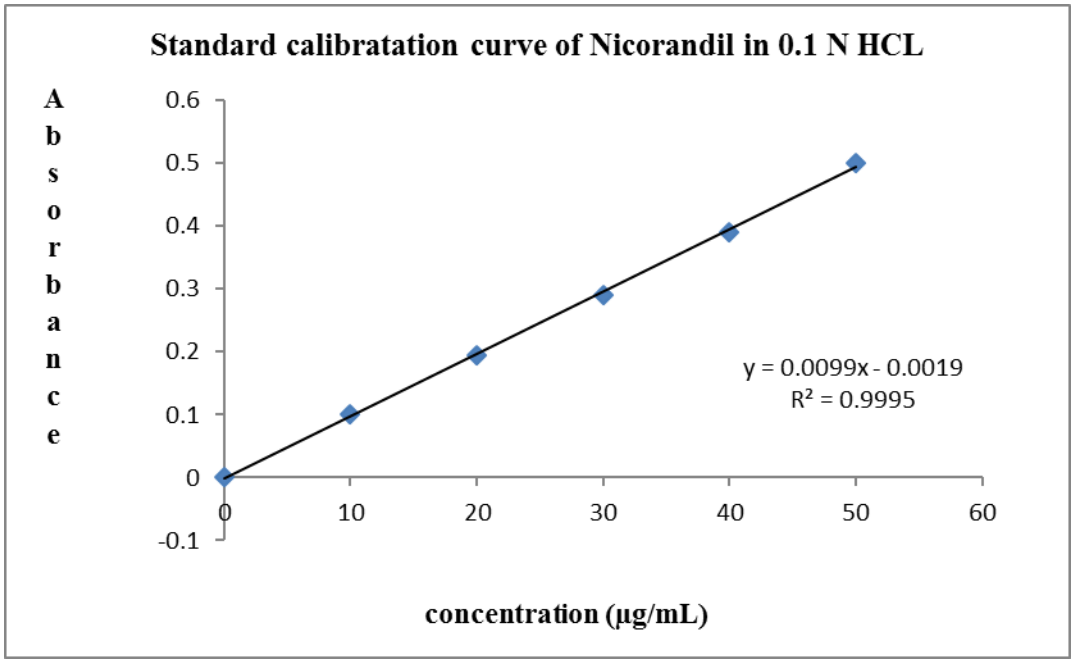

Figure No. 5: Calibration curve of Nicorandil in 0.1 N HCl buffer.

Evaluation of post-compression parameters of Nicorandil Controlled Release floating Tablets:

The preliminary studies were carried out by preparing various formulations with different process variables and subjecting the formulation to all post-compression parameters that have been fulfilled according to IP standards.

Weight variation:

The average weight of 20 tablets of Nicorandil was calculated for each formulation which varied from 295 ± 2 to 305 ± 3 mg. they complied with the official requirements as per IP.

Tablet hardness (kg/cm^2):

The hardness of the tablet developed formulation shows 6.1 ± 1.0 kg/cm^2 to 6.6 ± 1.0 kg/cm^2.

% Friability:

The friability of the developed formulation varied from 0.15 ± 0.1 % to 0.20 ± 0.01 % loss which was less than 1 % as per the official requirement of IP.

% Drug content:

The % drug content was found to be 99.1 to 104.3 %.

***In-vitro* Buoyancy and total Flotation test:**

From the results, it was observed that the buoyancy lag time and the total floating time were studied for all the formulations. F1, F2, F3, F4, F5, and F6 total floating times were found to be 12.50, 10.41, 9.3, 8.0, 8.4, 9.0 hrs. The formulations with natural gums showed Buoyancy lag. The formulation with a combination of polymers (F1) showed optimum buoyancy lag time. Therefore, with an add to in the attentiveness of the natural gums sum floating time was found to be greater than before owing to reduce in the solubility. Thus, polymer Guar gum, Almond gum, and the combination of Sodium bicarbonate were found to have optimum floating characters for a longer period.

Post–compression parameters:

Table No. 6: Post compression parameters Nicorandil Controlled Release floating Tablets

Formulation code	Weight Variation (mg)	Hardness (kg/cm^2)	% 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 of Nicorandil floating Controlled-Release Tablets:**

In-vitro dissolution study was performed by using USP type II dissolution test apparatus (paddle type) [Lab, India (DS-8000, Mumbai)] at 100 RPM. 900ml of 0.1N HCl buffer was used as the dissolution medium which was maintained at 37 ± 0.5ºC. Aliquots of dissolution medium (5mL) were withdrawn at specific time intervals (1, 2, 4, 6.8,10, 12, 16, 20, and 24 hr) and were filtered by micron filters. The amount of drug dissolved was determined by a UV- spectrophotometer by measuring the absorbance of the sample at 262 nm.

All six formulations are prepared by using different concentrations of polymers like guar gum and almond gum. F1, F2, F3, F4, F5, and F6 were prepared in different ratios of guar gum and almond gum control release. The drug released in formulation F1 is 91.23 % in 24 hr, F2 is 95.03 % in 24 hr, F3 is 98.23 % in 24 hr, F4 is 96.23 % in 24 hr, F5 is 97.86 in 24 hr and F6 formulation the drug released was 99.59 % in 24 hr.

In the optimized formulation F6, prepared with almond gum the dissolution medium was 900 ml of 0.1 N HCl buffer and the drug released in formulation F6 is 99.59 % in 24 hr.

Table No. 7: Dissolution studies for Nicorandil Controlled Release floating Tablets.

Dissolution with 0.1N HCL 900 ml, RPM 100, λ max 262 nm							
% Cumulative Drug Release							
Sr. 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

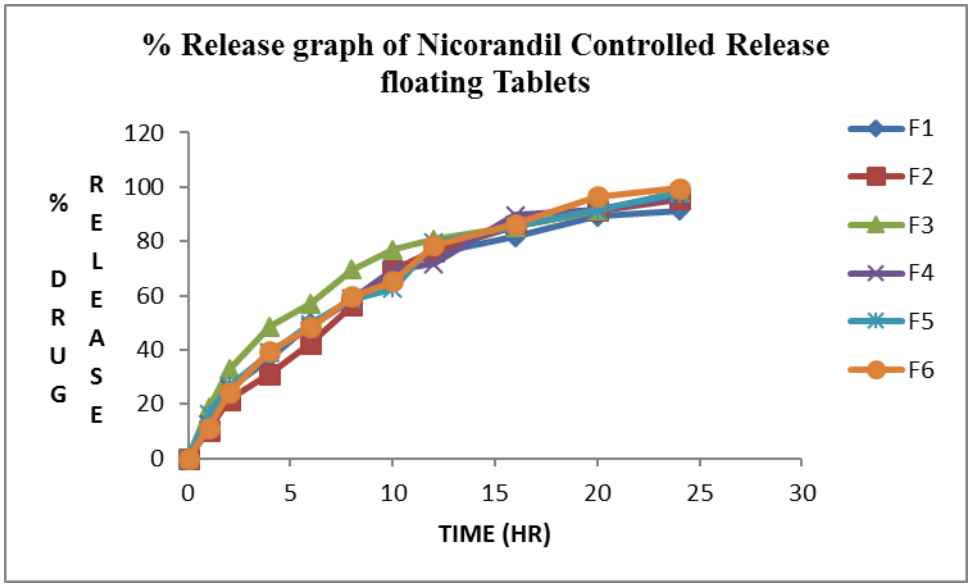

Figure No. 6: %Release graph of Nicorandil Controlled Release floating Tablets with guar gum and almond gum (F1 - F6).

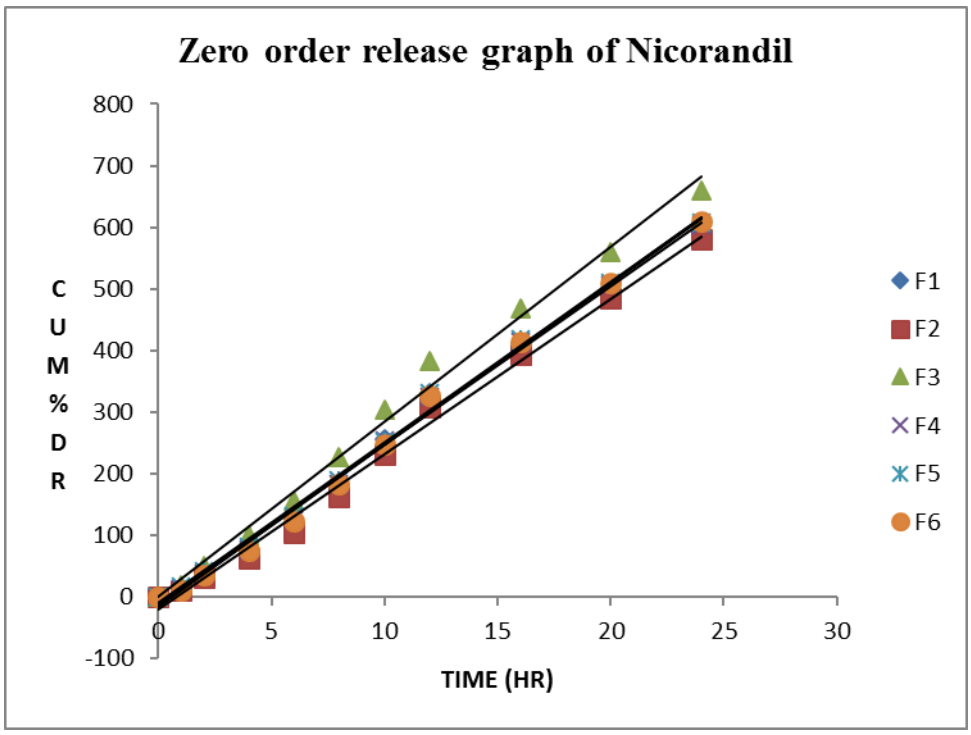

Figure No. 7: Zero-order release graph of Nicorandil Controlled Release floating Tablets with guar gum and almond gum (F1 - F6).

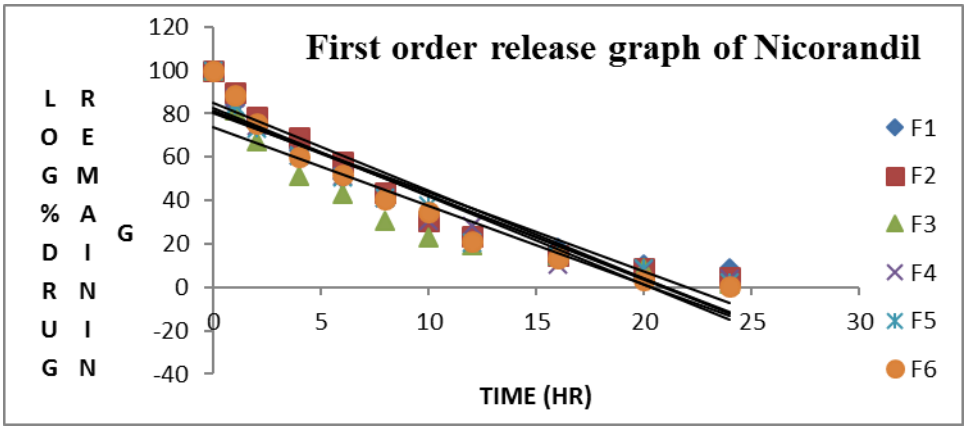

Figure No. 8: First order release graph of Nicorandil Controlled Release floating Tablets with guar gum and almond gum (F1 - F6).

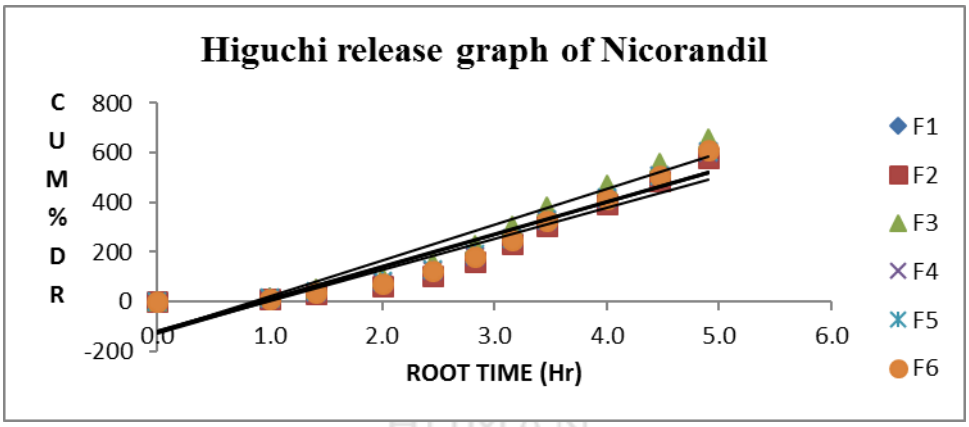

Figure No. 9: Higuchi release graph of Nicorandil Controlled Release floating Tablets with guar gum and almond gum (F1 - F6).

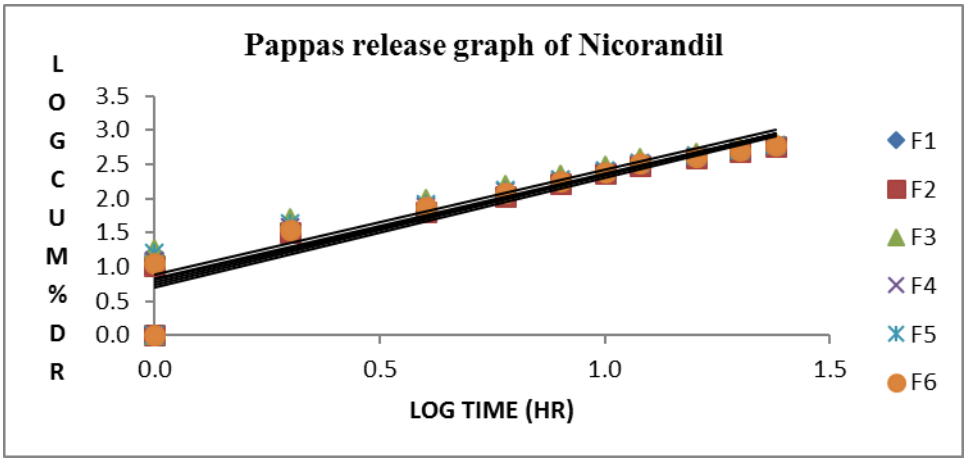

Figure No. 10: Pappas release graph of Nicorandil Controlled Release floating Tablets with guar gum and almond gum (F1 - F6).

Curve-Fitting Analysis:

According to different kinetic models, the kinetics of the F1 and F6 drug release was evaluated by drug release rate models namely zero-order, first-order kinetics, and Higuchi, papas mechanisms. The dissolution kinetics data have defected. The optimized formulation F6 showed the highest r value i.e. 0.996 for zero-order plots indicating that release of drug follows zero-order kinetics, and mechanism of release was fitted to Higuchi equation with the r-value of 0.904 indicating anomalous fickian diffusion mechanisms and may indicate that the drug release is higher by more than one process.

Table No. 8: Dissolution kinetics of Nicorandil Controlled Release floating Tablets with guar gum and almond gum (F1 - F6).

Correlation coefficient				
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

CONCLUSION:

The present work described the pre-formulation and formulation development that led to the production of Nicorandil controlled release floating tablets by direct compression of a homogeneous powder blend/granules. To achieve the drug release up to 24 hrs, studies have been carried out on direct compression method by the use of natural polymers (guar gum and almond gum). The results indicated that the polymer combination showed maximum drug release retarding ability than individual polymers. As such the floating tablets were prepared for oral controlled delivery of Nicorandil. The aim of the present work was completely fulfilled by the use of guar gum and almond gum as the drug release was extended up to 24 hrs. Further, drug release data were interpreted to determine the order, mechanism, and drug release behavior from the dosage form. The results revealed that the drug release from the optimized formulation follows zero-order kinetics and Higuchi kinetic model. The release kinetics of the optimized formulation was the best fit with the Korsmeyer-Peppas model.

Further, the drug release data was used to predict the deviation from the respective ideal release profile and the results revealed that the release profile of the optimized formulation was slightly below their ideal release profile. The following conclusions were drawn from the present investigation. The Nicorandil was compatible with guar gum, almond gum, and cetostearyl alcohol. A shorter floating lag time was observed. The drug release rate from the floating tablets can be changed with guar gum and almond gum ratio. The drug release rate from the floating tablets can be achieved with guar gum and almond gum ratio. The optimized formula (F6) has fulfilled my objective. The drug release was found to be 99.59 % in 24 hr. Gas generating agent (effervescent) concentration controls the floating properties of the tablets. The size of the granules influences the drug release characteristics from Nicorandil floating tablet dosage form.

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