Section A-Research paper

FORMULATION DEVELOPMENT AND EVALUATION OF MUCOADHESIVE DRUG DELIVERY SYSTEM

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ABSTRACT: Nicardipine is a calcium channel blockers which blocks the influx of calcium ions into smooth muscles and blocking the influx of calcium ions which results in a vasodilation and decrease the oxygen consumption and reduce the cardiac load. Nicardipine is used in the treatment of hypertension and angina pectoris and also used for management of heart failure. Aim of the present work is to formulation and evaluation of mucoadhesive tablets of Nicardipine using natural binders such as Gum tragacanth and Guar Gum to reduce the first pass metabolism and frequency of administration. HPMC was used as polymer Gumtragacanth and Guar Gum used as swelling agent as well as control release polymer.
The tablets were formulated by direct compression method and were then evaluated for various pre-compression and post compression parameters such as hardness, friability, thickness, weight uniformity, drug content, drug release, swelling study, in-vitro drug release and in-vitro mucoadhesive strength.
FTIR showed no interaction between drug and polymers. The optimized formula consisted of Nicardipine (30mg), Chitosan Gum Tragacanth and gaur gum, showed a maximum drug release after12 hrs,maximum swelling was attained in 8hrs and the highest mucoadhesive strength. Results indicate that release from optimized formulation of mucoadhesive buccal tablets of Nicardipine fits zero order kinetics and can by-pass the first pass metabolism and enhance the release of drug for extended periodoftime.

Keywords: Nicardipine, Mucoadhesive Tablets, GuarGum, Chitosan, Mucoadhesive Strength Etc.

1. INTRODUCTION

Oral controlled drug delivery's primary goal is to provide tablets for longer periods of time in order to achieve greater bioavailability, which should be foreseeable and repeatable. However, it is challenging because of a variety of physiological difficulties, such as variations in the gastric emptying process, a small absorption window, and gastrointestinal stability issues[1]. Unique strategies to keep the dosage form in the stomach have been presented as a solution to those issues. These include delayed gastric emptying devices such as floating systems, mucoadhesive or bioadhesive systems [2], swelling and increasing systems [3, 4] and rising systems [5]. A mucus membrane's tendency to "stick" to an organic or synthetic material, which causes the fabric to adhere to the tissue for an extended period ofa mucus membrane's tendency to "stick" to an organic or synthetic material, which causes the fabric to adhere to the tissue for an extended period of time, is known as mucoadhesion or bioadhesion Oral controlled drug delivery's main goal is to provide pills for long-term use. A cloth needs to interact with the mucus, a highly hydrated, viscous anionic hydrogel layer defending the mucosa, in order to become bioadhesive.

The mucoadhesive coaching principle offers a straightforward, practical method that is very useful for extending a dose form's duration in the stomach, improving the drug's oral bioavailability. Most mucoadhesive substances are either manufactured, natural, hydrophilic, or insoluble in water polymers that have the ability to make many hydrogen bonds because they include hydroxyl, carboxyl, or sulphate functional groups.[6]

Binders are salespeople who provide the granules cohesion. This ensures that the tablet willbe unaffected by compression. In order to achieve various tablet mechanical electricity and drug release dwellings for specific pharmaceutical purposes, specific binding retailers might be helpful. Herbal binders such particular starch, gums, mucilages, and dried fruit have the ability to bind in addition to having other properties like filler and disintegrant, and they are safer and less expensive than synthetic polymers like PVP.[7]

Nicardipine belongs to the group of drugs known as calcium channel blockers. By allowing the blood arteries to relax, it decreases blood pressure and lessens the workload on the heart's pumping action. By boosting the flow of blood and oxygen to the heart, it alleviates chest pain. The bioavailability of nicardipine was between 15 and 45 percent at doses between 10 and 40 mg.[8]

Nicardipine is prescribed to treat excessive blood pressure and to manage angina (chest pain). The bioavailability is set to be between 15 and 40%, while the removal half-life is fixed at five hours. This is as a result of the drug's current mechanism, which skips liver and intestinal wall metabolism first[7]. Because it has a plentiful blood supply and is quite porous, the buccal mucosa is an appealing route for the systemic delivery of many pills[8,9]. Compared to conventional methods of systemic medication administration, the mucoadhesive buccal drug delivery system has many advantages[10].

2. MATERIALS ANDMETHODS

2.1 Materials

Dhamtech Pharma provides nicardipine. Chitosan and guar gum are both available from ajanta pharma Aurangabad as well as Encore health pvt.Ltd. The additional chemicals and reagents that were employed were all analytical reagent grade.

2.2 PreparationofMucoadhesive TabletsofNicardipine

Nicardipine mucoadhesive tablets were made utilising the direct compression method and the polymers chitosan, HPMC K4M, sodium alginate, gaur gum, and gum acacia. According to the batch formula (Table), all of the constituents, including the medication, polymer, and excipients, were precisely weighed. With the use of a stainless steel spatula, the medication and all the other materials aside from the lubricants were transferred to a sheet of butter paper. The ingredients were then combined in descending weight order and blended for 10 minutes in an expanded polyethylene pouch. The lubricant was added and well mixed for two minutes after the ingredients had been thoroughly mixed. On a single stroke tablet punching machine, the prepared blend of each formulation was pre-compressed using various punches (8mm and 9mm) in accordance with their weights (Rimek) to create a mucoadhesive tablet, apply pressure of 0.5 tonnes and turret speed of 2 rpm.

Table 1: Formulation of single mucoadhesive tablet of Nicardipine

Ingredients mg/tablet	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nicardipine	30	30	30	30	30	30	30	30	30
HPMC	30	20	20	31	10	30	20	10	8
Sod. Alginate	10	05	05	10	15	10	-	10	10
Gum Tragacanth	20	10	25	20	15	10	20	20	20
Gaur gum	20	15	20	20	15	15	15	20	20
Chitosan	10	08	20	20	10	10	10	30	20
MCC	73	105	73	61	98	88	76	73	85
Mg. Stearate	5	5	5	5	5	5	5	5	5
Talc	2	2	2	2	2	2	2	2	2
Total	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

3. EvaluationTests

3.1 Characterization of mucoadhesive tablets of Nicardipine:

1. Polymer drug interaction study:

The drug-polymer and polymer-polymer interplay became studied by way of FTIR spectrometer the use of Shimadzu 8400-S, Japan. percentage (w/w) of the pattern with recognize to a potassium bromide disc changed into combined with dry KBr. The combination changed into ground into a excellent powder the use of an agate mortar and then compressed into a KBr discs in a hydraulic press at a stress of 10000 psi. Each KBr disc turned into scanned 16 times at 2 mm/sec at a resolution of 4 cm–1 the usage of cosine apodization. The characteristic peaks had been recorded.

I. Evaluation of mucoadhesive tablets of Nicardipine:

1) Hardnesstest[11]:

Using a Monsanto Hardness tester, the tablets' hardness was assessed. Kg/cm2 is the unit of measurement. From each formulation, three tablets were chosen at random, and the mean and standard deviation values were computed.

2) Thickness[11]:

Sing a Vernier Capillar and three randomly chosen tablets from each recipe, the thickness was measured in mm.

3) Friabilitytest[11]:

When exposed to mechanical shock or attrition, it is a condition where tablet surfaces are harmed and/or show signs of lamination or fracture. Using the Roche Friabilator and the IP friability technique, the friability of the tablet was ascertained. It's stated as a percentage (%). Twenty pills were placed in the friabilator after being originally weighed (Winitial). The friabilator was run up to 100 revolutions per minute or at 25 rpm for 4 minutes. Again weighing the tablets was done (Wfinal). Tablets with less than 1% friability are acceptable.

4) Uniformity ofweight[12,13]:

The weight variation test was carried out in accordance with IP protocol. Dusting off each tablet and setting it in an electronic balance allowed us to determine the weight (in mg) of each of the 20 unique tablets that were randomly chosen from each formulation. The sample mean and % deviation were calculated using the weight data from the pills.

5) Uniformity of drugcontent[12,13]:

Five pills were crushed in a glass mortar to a powder, and 50 mg of the resulting powder was added to a 100 ml conical flask with a stopper. The drug was extracted using 40 ml of methanol and vigorous shaking for an hour at 100 revolutions per minute on a mechanical gyratory shaker. After 30 minutes of heating on a water bath with periodic shaking, the mixture was filtered through cotton wool into a 50 ml volumetric flask. The filtrate was then diluted appropriately and the absorbance at 235nm was measured in comparison to a blank (methanol).

6) SwellingIndex[15]:

In phosphate buffer pH 6.8, the swelling index of the mucoadhesive pill was assessed. The tablet's original weight was calculated, and it was then put in a petridish with 6 ml of phosphate buffer, pH 6.8, and incubated at 37 °C. At various time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, and 8.0 h), the tablet was withdrawn, blotted with filter paper, and reweighed (W2). The formula below is used to compute the swelling index:

Swelling index = $100\ (W_2\text{-}W_1) / W_1$.

Where, W_1 = Initial weight of the tablet.

W_2 = Final weight of tablet.

7) Mucoadhesionstrength[19]:

Ex vivo residence time was used to determine the adhesive strength of a mucilage tablet, and the apparatus

was modified from a USP dissolving test setup. After being secured on a glass slab for 30 seconds, the test and control mucilage tablets (200mg) were applied to the excised goat mucosa and submerged in a jar of dissolution equipment containing 750 mL of phosphate buffer, pH 6.8 at 37 °C. The USP dissolving equipment' paddle type II device was set at a distance of 5 cm above the tablet and revolved at a speed of 25 rpm. It was noted when the mucosa completely eroded or detached.

8) Short Term Stabilitystudies[22]:

The promising mucoadhesive Nicardipine tablets were subjected to a short-term stability investigation over three months (90 days) at a temperature of 40.2° C. A sufficient number of tablets (10) were packed in amber-colored screw-cap bottles and individually wrapped in aluminium foil before being maintained in a stability chamber for three months. Each month, samples were collected for analysis of the drug content, surface pH, and in vitro drug release studies.

4. RESULTS AND DISCUSSION:

4.1 Melting pointdetermination

Melting point of Nicardipine was obained in the range of 171-172^{0}C. The standard melting point value of Nicardipine is 172^{0}C.

4.2 Drug-polymer interaction studies byFT-IR

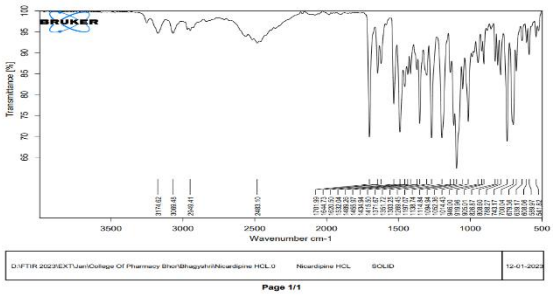

Fig 1: IR Spectrum of Nicardipine.

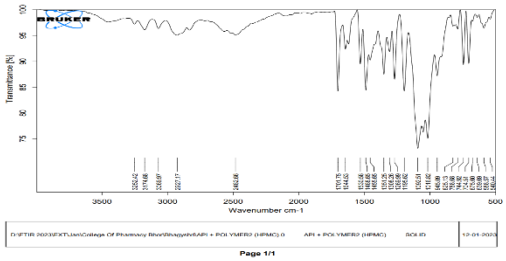

Fig 2: FTIR Spectra of Nicardipine:HPMC.

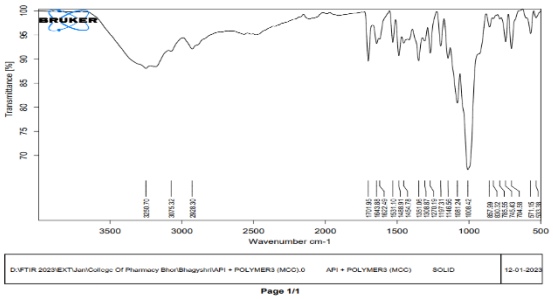

Fig 3: FTIR Spectra of Nicardipine:MCC.

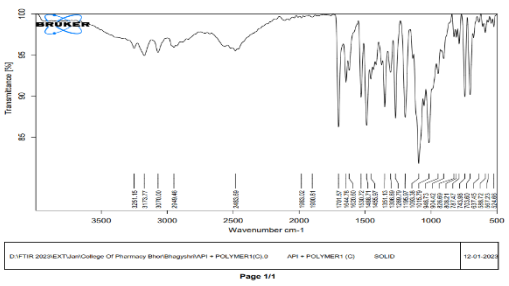

Fig 4: FTIR Spectra of Nicardipine:Chitosan.

This study show that all drug and excipient are compatible with each other. There is no impurities or interaction are seen in Drug and excipients.

4.3 Evaluation of powder properties (Pre-compression parameters)

Table No.2.bulk density and tapped density of the powder formulation

S.No of Formulation	Bulk Density	Tapped Density	Angle of Repose	Hauser's Ratio	Carr's Index
F1	0.4477±0.005	0.5357±0.008	24°.47±0.013	1.1965±0.017	16.42
F2	0.4580±0.006	0.5357±0.008	23°.98±0.149	1.1696±0.016	14.50
F3	0.4284±0.005	0.4918±0.007	22°.83±0.396	1.1479±0.002	12.89
F4	0.4511±0.005	0.5218±0.077	22°.53±0.334	1.1567±0.002	13.54
F5	0.4313±0.005	0.4839±0.006	21^0.69±0.439	1.1219±0.025	10.87
F6	0.4285±0.005	0.4979±0.006	21^0.31±0.234	1.1619±0.017	13.93
F7	0.4651±0.006	0.5313±0.007	20^0.43±0.135	1.1423±0.032	12.46
F8	0.4285±0.005	0.4763±0.011	20°.93±0.313	1.1115±0.030	10.03
F9	0.4175±0.005	0.4819±0.005	21^0.69±0.439	1.1429±0.002	11.87

The values obtained lies within the acceptable range. All the parameters are within rage so it is suitable for direct compression method.

4.4 Post compressionparameters:

4.4.1 Shape of thetablets:

Visually inspection of prepared all tablets were done. The shapes of the tablets were found to be good.

4.4.2 Friability(F)

All of the formulations' friability levels were under 1%, which shows that they were all within the permitted ranges. The tablet has good mechanical strength, according to the friability test results. The range of the friability value is 0.67 to 0.92.

4.4.3 Hardness:

The results were tabulated in Table no 8.8. The hardness value ranges from 4.97± 0.032 to 6.93± 0.133kg/cm^2.

4.4.4 Weightvariation:

The data were pretty uniformly acquired. The dosages of the pills range from 198.9 mg to 199.8 mg. Since the weight fluctuation was less than 8.5% of the weight allowed by the Pharmacopoeia, all of the pills passed the weight variation test.

Formulation Code	Friability (%)	Hardness (kg/cm2)	Weight Variation(mg) (n=20)
F1	0.88	6.42± 0.0421	199.5± 1.865
F2	0.83	6.23± 0.121	198.6± 1.371
F3	0.87	6.29± 0.121	198.9± 1.452
F4	0.77	5.99± 0.111	199± 2.258
F5	0.88	5.85± 0.113	198.9± 1.492
F6	0.68	5.54± 0.119	198.7± 1.531
F7	0.87	5.35± 0.046	198.9± 1.786

F8	0.92	5.23± 0.075	199.3± 1.942
F9	0.88	6.29± 0.121	198.9± 1.452

Table no 3: Post compressional parameters of gastro retentive mucoadhesive tablet of Nicardipine

4.4.5 Thickness

The micrometre (mm) unit of measurement for tablet thickness was used. The tablet's thickness suggests that the die fill was consistent. Punches are 8 mm in diameter, and each pill weighs 200 mg, therefore these factors together determine the thickness. Each formulation's average weight was noted and is displayed in Table 8.8. Thickness values range from 2.839 0.026 to 3.129 0.043 mm.

4.4.6 Uniformity of drug content:

All of the developed pills' drug contents were found to be within the permitted range. Nicardipine's drug content percentage ranged from 94.89 to 99.24percent.The findings within the range show that the mixing was uniform. The table displays the percentage of drugs in each formulation.

Tableno 4: Post compressional parameters of gastro retentive mucoadhesive tablet of Nicardipine

Formulation Code	Thickness (mm) (n=3) Mean±S.D	Drug Content (%) (n=3) Mean±S.D
F1	2.969± 0.038	98.98± 1.154
F2	2.839± 0.026	96.27± 0.891
F3	2.929± 0.021	98.59± 0.672
F4	3.049± 0.039	98.40± 0.866
F5	2.969± 0.054	98.59± 0.865
F6	3.129± 0.043	96.82± 0.861
F7	2.919± 0.021	98.43± 0.869
F8	2.959± 0.047	99.24± 0.586
F9	3.047± 0.040	97.90± 0.856

4.4.7 Swelling study

Swelling index testing was done for the initial formulation, and the results are displayed in the table. The findings of the evaluation of the swelling index of the tablets from each formulation (F1 to F9) are shown in Table 5.

Table no 5 % swelling index for polymer gastro retentive mucoadhesive tablet of Nicardipine

FORM. CODE	30 min	1Hrs	2 Hrs	3 Hrs	4 Hrs	5Hrs	6Hrs	7Hrs	8Hrs

F1	41.15± 0.304	50.7625± 0.40 2	60.375± 0.306	62.9875± 0.385	67.75±0 .3010	76.25±0.4 02	79.6±0.3 32	81.48±0 .363	118.05± 0.341
F2	90.75± 0.310	99.07±0.3 06	108.39± 0.152	115.71±0. 203	120.75± 0.210	129.07±0. 306	131.03± 0.123	141.48± 0.363	141.31± 0.203
F3	34.98± 0.306	43.46125 ±0.541	51.9425 ±0.352	60.42375 ±0.102	90.75±0 .3110	93.46125 ±0.54 1	98.905± 0.312	99.48±0 .363	102.83± 0.230
F4	72.17± 0.345	79.675±0. 158	88.18±0. 415	94.685±0. 446	95.75±0 .0210	97.675±0. 158	102.19± 0.701	110.48± 0.363	132.21± 0.562
F5	32.61± 0.366	40.81875 ±0.211	49.0275 ±0.322	58.23625 ±0.374	62.75±0 .0210	70.81875 ±0.21 1	75.445± 0.385	79.48±0 .363	98.28±0 .341
F6	62.36± 0.396	69.7875± 0.346	78.215± 0.304	84.6425± 0.455	90.75±0 .050	93.7875± 0.346	99.07±0. 263	100.48± 0.363	121.78± 0.340
F7	32.94± 0.501	41.56125 ±0.420	50.1825 ±0.230	58.80375 ±0.32 1	60.85±0 .210	61.56125 ±0.420	68.425± 0.340	78.48±0 .363	101.91± 0.355
F8	58.73± 0.930	65.69875 ±0.800	73.6675 ±0.813	81.63625 ±0.503	86.65±0 .0310	90.69875 ±0.800	121.605 ±0.179	130.48± 0.363	155.48± 0.363
F9	72.17± 0.803	79.675±0. 206	88.1±0.3 18	94.685±0. 206	96.75±0 .310	98.675±0. 206	101.19± 0.506	102.48± 0.363	117.98± 0.300

4.4.8 In vitrodissolution

Utilising the USP XXIII dissolution test apparatus-II at 50 rpm and 900 mL of 6.8 pH buffer kept at 37 0.5 oC as the dissolve medium, in vitro drug release tests were carried out. Preliminary formulations' in vitro drug release profiles were compiled in Table No. 1 of in vitro dissolution investigations of polymer formulations. Figure shows the cumulative percentage medication release plotted against time (Hr) for early formulations.

Table no 6: % Cumulative drug release of polymer gastro retentive mucoadhesive tablet of Nicardipine (F1-F5)

Time (Hrs)	**F1**	**F2**	**F3**	**F4**	**F5**
1	18.923±1.591	14.583±0.520	16.840±1.310	13.888±1.310	10.651± 1.172
2	21.806±0.299	19.872±1.565	20.753±1.588	25.424±1.681	20.190±0.306
3	25.120±1.378	23.721±0.608	24.073±0.910	29.481±1.600	22.363±0.522

4	28.611±1.091	26.867± 1.087	26.695±1.379	36.100±1.386	26.789± 0.302
5	31.408±0.907	29.662±1.208	29.835±1.385	42.039±1.598	34.817±0.527
6	34.722±0.800	32.455±1.384	33.151±1.598	50.406±1.598	38.158±0.521
7	38.212±0.906	35.042±1.511	35.773±1.600	55.139±1.315	42.682±1.565
8	41.357±0.907	38.042±1.682	38.392±1.093	66.624±0.802	43.659±0.804
9	44.673±0.800	41.529±1.512	41.531±1.316	75.368±1.566	45.974±1.283
10	48.295±1.206	45.021±1.386	44.500±0.528	81.493±1.837	48.912±1.191
11	54.775±1.316	50.943±1.091	49.898±1.594	88.082±0.801	56.778±0.801
12	57.673±0.800	51.529±1.512	50.531±1.316	90.368±1.566	60.974±1.283

Table no 7: % Cumulative drug release of polymer gastro retentive mucoadhesive tablet of Nicardipine (F6-F1)

Time (Hrs)	**F6**	**F7**	**F8**	**F9**
1	9.722± 1.084	16.145± 1.877	18.708± 1.041	11.651± 1.172
2	18.109±0.304	23.527±0.510	22.841± 0.305	20.190±0.306
3	20.933±0.520	31.081±0.798	24.952± 1.379	22.363±0.522
4	24.768± 0.300	40.016±0.304	39.304± 0.542	26.789± 0.302
5	29.824±0.520	44.888±0.796	42.627± 1.086	34.817±0.527
6	32.977±0.523	58.213±0.525	59.249± 0.800	38.158±0.521
7	38.682±1.565	63.266±0.798	69.430± 0.799	42.682±1.565
8	40.659±0.804	72.898±0.800	72.579± 0.799	43.659±0.804
9	43.974±1.382	78.253±0.525	80.895± 0.605	45.974±1.283
10	48.812±1.091	81.444±0.523	85.906± 0.798	48.912±1.191
11	54.778±0.801	83.932±1.086	89.974±1.382	59.778±0.801
12	56.977±0.523	87.213±0.525	95.525± 0.905	38.158±0.521

4.4.9 *In vitro* mucoadhesivestrength:

Utilising a modified version of a USP dissolving test device, in vitro mucoadhesive strength tests were conducted. Table no. 8.13 displays the results for in vitro mucoadhesive strength and adhesion force. The mucoadhesive strength of F8 was much higher than that of other formulations, but it is significantly weaker than that of F9, which is the industry standard.

Table no: 8: Mucoadhesive strength of polymer gastro retentive mucoadhesive tablet of Nicardipine

Formulation No.	Mucoadhesive strength (g)	Mucoadhesion force (N)
F1	23.471	2.302036
F2	22.300	2.187184
F3	22.720	2.228378
F4	21.350	2.094008
F5	20.580	2.018486
F6	23.890	2.343131
F7	24.576	2.354254
F8	25.240	2. 419634
F9	21.280	2.094008

4.4.10 Stabilitystudy:

The accelerated stability studies were carried out according to ICH guidelines. Optimized formulations F8 were packed in amber color bottle and aluminum foil laminated on the upper part of the bottle and these packed formulations were stored in ICH certified stability chambers. Maintained at $40^0C \pm 2^0C$ (zone III conditions as per ICH Guidelines) for 3 months. The tablets were evaluated before and after one month for change in appearance, the drug content and *in vitro* release.

After a period of one month, the samples were observed for any change on appearance. It was observed that tablet was devoid of any change in color or appearance of any kind of spot on it. It was also noted that tablet was free of any kind of microbial or fungal growth or bad odor. The formulation batch showed circular shape with no cracks. The drug content of the formulation F8 was found to be 98.83 %, 98.19% and 99.92 % at interval of 30 days respectively. The %CDR of formulation F8 was found to be 94.16%, 93.98% and 93.82 % at interval of 30 days respectively.

Table no 8.14: Stability study for F8

Time (days)	Physical Appearance	Drug content	% CDR
30	No change	98.83%	94.16
60	No change	98.19%	93.98
90	No change	99.92%	93.82

Study of different evaluation parameters of optimized batch (F8) after stability study:

Sr. No.	Parameters	40^oC 75% RH
1	Friability	0.24%
2	Hardness	3.3 Kg/cm^2
3	In-vitro release	99.95%

4	Swelling Index	90.51%
5	Mucoadhesive Strength	20.796

CONCLUSION:

The goal of the current study was to develop a mucoadhesive drug delivery system for the oral anti-diabetic medication nicordinpine in order to increase its oral bioavailability and provide sustained drug release for a longer period of time. According to the experimental findings, Nicardipine mucoadhesive drug delivery systems can be made utilising the direct compression approach and a variety of polymers, including Chitosan, Gurgum, Tragacanth, and HPMC gum. A suitable technique for drug analysis using UV spectrophotometry was created. In phosphate buffer at pH 6.8, nicotripine exhibited maximum absorption at a wavelength of 235nm. Since the regression coefficient (r2) was found to be 0.999, it was clear that concentration and absorbance had a linear relationship. Studies using IR spectroscopy revealed that there isin the developed formulations, there was no drug-polymer interaction. Final formulations were created utilising mixtures of two or three polymers based on developed preliminary formulations. It was discovered that none of the manufactured tablet formulations had capping or chipping. This study came to the conclusion that when gum content increases, so does the swelling index. Compared to other polymers, guar gum was found to cause higher edoema. Gaur gum is swollen more than tragacanth gum or chitosan, in that order. The majority of the Nicardipine Mucoadhesive Drug Delivery System formulations showed zero order release kinetics, and the drug release is governed by a non-Fickanian diffusion mechanism. This study came to the conclusion that the in vitro mucoadhesive strength increases as gum concentration increases. Chitosan demonstrated increased mucoadhesivestrength. Gaur gum is the strongest mucoadhesive, followed by tragacanth gum and chitosan. Studies on the short-term stability of optimised formulations F7 indicates that after one month of storage at 400C 20C and 75% RH 5%, there have been no appreciable changes to the drug content or dissolving parameter values.

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