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DESIGN, DEVELOPMENT AND EVALUATION OF BILAYER TABLET OF NIMODIPINE AS IMMEDIATE RELEASE AND METFORMIN AS CONTROLLED RELEASE

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ABSTRACT

The aim the study is to formulate Bilayer tablets of Nimodipine and Metformin. Nimodipine as immediate release to lower the blood pressure and metformin as controlled release layer for type 2 diabetes mellitus. Nimodipine is a calcium channel blocker used to prevent "vasospasms" include cerebral ischemia. Metformin ability was to suppress the production of glucose in liver and increase the absorption of glucose intake in gut wall. Crospoidone as superdisintegrant nimodipine layer is developed with direct compression. The controlled release of metformin layer was prepared by using polymers like HPMC K-100M, SCMC, sodium alginate, and Eudragit RLPO, RS100, RSPO. These formulations were prepared by wet granulation method and compressed using 19 mm punch of 16 station rotary press. The prepared granules were evaluated by pre and post compression parameters like bulk density, tapped density, Carr's index angle of repose, Hausner's ratio, Friability, hardness, thickness, weight variation, drug content and in vitro dissolution. The FTIR studies shows that no interaction between drug and excipients. The nimodipine layer releases immediately within 15 min. Metformin controlled release layer of F9 Formulation release 85.15% up to 20 hrs. The best fit formulations subjected for stability studies showed no significant changes stored at 45c /75RH for 1 month according to ICH guidelines.

Keyword: Nimodipine, metformin, type 2 diabetes mellitus, bilayer, wet granulation method

INTRODUCTION:

Oral drug delivery systems (DDS) are the patient friendly systems designed for oral administration. These systems can be categorized as conventional drug delivery systems and modified drug delivery systems. Conventional drug delivery dosage forms are used for instant drug release. More often these systems results fluctuations in plasma drug levels that lead to reduction in drug effectiveness or increased incidence of side effects. So, in order to compensate the decrease in drug plasma concentration due to metabolism and excretion, there is need to administer such systems more than once a day. Oral modified drug delivery systems are being developed to produce more reliable absorption with increased bioavailability and to improve the efficacy of the drug either by controlling its release for a prolonged period or by enhancing its release rate. These drug delivery systems improve the pharmacokinetic profile of the drug and patient compliance by minimizing the frequency of dosing and the dose dependent side effects. Oral MDDS can be formulated to releases one or more drugs continuously in a predetermined pattern for a fixed time period. Gastro Retentive Drug Delivery Systems (GRDDS) are the controlled release dosage forms that retain in the stomach for several hours which would significantly prolong the gastric residence time (GRT) of drugs. These systems improve bioavailability and reduce wastage of drug. It delivery to proximal small intestine as well as stomach. An increasingly popular dosage form known as a bilayered tablet, which includes two or more active pharmacological components, has been developed by the pharmaceutical industry during the past ten years. The convenience and compliance of patients have been greatly improved by this development. With each medicine having a different release profile, such as an instant release or a prolonged release, these cutting-edge drug delivery systems mix many medications into a single unit. As a result, this strategy enables prolonged drug activity and enhanced control over plasma drug levels. Due to the use of different ingredients and complex geometric boundaries between the two adjacent layers; it requires a complicated tablet structure along with patient friendly administration which poses serious challenges to pharmaceutical scientists.

MATERIALS AND METHODS:

Analytical method for Nimodipine by UV spectrophotometer:

By the spectral analysis through a UV-visible spectrophotometer, the wavelength at

which Nimodipine shows maximum absorbance was determined.

Preparation of standard stock solution of Nimodipine pure drug:

Nimodipine's standard medication solution was made by combining 10 mg of nimodipine with 10 ml of pH 6.8 Phosphate buffer with 0.05% w/v SLS giving a stock solution containing 1000 g/ml in a volumetric flask. 1ml of stock solution was taken out and diluted further with 0.05% w/v SLS in a pH 6.8 phosphate buffer to produce a stock solution with a 100 µg/ml concentration **[1]**.

Preparation of different concentrations of standard stock solution of Nimodipine:

By employing pH 6.8 phosphate buffers, the stock solution was diluted to generate concentrations ranging from 5 to 25 µg/ml. The analysis revealed that the wavelength of 238.5 nm exhibited maximum absorbance ("λmax") for accurately estimating the concentration of nimodipine. The calibration curve was presented in **Tables 9**, along with **Figures 6 and 7**, utilizing different buffers.

Placebo interference:

The excipients used in the formulation may interference with the absorbance at the same wavelength at which the drug shows maximum absorbance. Hence it is very importance to check the placebo interference.

Preparation of placebo sample:

The placebo blend was prepared by weighing the composition required for 10 Nimodipine tablets without the active ingredient. This consists of 62.5mg of crospovidone, 250mg of calcium carbonate, 10mg of aerosol, 312.5mg of lactose monohydrate (flowlac), 514.5mg of MCC PH101, 5mg of magnesium Stearate 5mg, 50mg of sodium bicarbonate, 6.25mg of polysorbate80, 6.25mg of SLS, 62.5mg of HPC-L, 3.125mg of sunset yellow. The ingredients were thoroughly blended in a polybag for a duration of 15 minutes. Following this, precisely 25 mg of the placebo blend was weighed and transferred to a 100 ml volumetric flask. Subsequently, 25 ml of methanol was added to the flask, thoroughly mixed, and subjected to sonication for approximately 30 minutes. The remaining volume was made up to 100ml with respective buffer and shacked well. The obtained solution was then centrifuged for 5min at 3500rpm. 4ml of the supernatant solution was pipette out and transferred to 100 ml volumetric flask and the volume was made up to 100ml with respective buffer (6.8pH phosphate buffer and 0.1N HCl). It was analyzed at 241nm using UV spectrophotometer. The aforementioned procedure was replicated six times. The

absorbance of the placebo blend in pH 6.8 phosphate buffer was found to be 0.0003±0.0002, while in 0.1N HCl, it was 0.0002±0.0001. These values indicate that the placebo sample exhibited negligible absorbance. Based on these findings, it was determined that the absorbance of the placebo did not interfere with the absorbance of Nimodipine at 238.5 nm.

Analytical method for Metformin using UV spectrophotometer:

By the spectral analysis through a UV-visible spectrophotometer, the wavelength at which Metformin shows maximum absorbance was determined.

Preparation of standard stock solution of Metformine pure drug:

The process involved weighing 100 mg of Metformin HCL and transferring it into individual 100 ml volumetric flasks. Subsequently, the drugs were dissolved in 50 ml of distilled water using sonication. The remaining volume was then filled with the same solvent to reach the mark on the flask, resulting in a final concentration of 1000 µg/ml for the Metformin HCL component **[2]**.

Preparation of different concentrations of standard stock solution:

Accurately pipetted out 0.5, 1 1.5, 2.0 and 2.5 ml of the solution mentioned above. Transferred them into separate dried volumetric flasks with a capacity of 100 ml each. To obtain concentrations of 5, 10 15 20 and 25 µg/ml respectively I filled each flask up to the mark with a solution of 0.1N HCL. Afterward I scanned the sample with a wavelength range of 200.0 to 400.0 using a scan speed. The maximum absorbance was obtained at 234nm wavelength. The calibration curve of metformin was given in the **Table 9 and Figures 6, 7** respectively.

Placebo interference:

The excipients used in the formulation may interference with the absorbance at the same wavelength at which the drug shows maximum absorbance. Hence it is very importance to check the placebo interference.

Method:

Except for the active component, all of the ingredients used to make Metformin tablets were precisely measured for 10 tablets. This placebo mixture contains 2500 mg HPMC, 1000 mg sodium bicarbonate, 30 mg aerosol, 30 mg talc, 300 mg each of the following: Eudragit RLPO, Eudragit RSPO, Eudragit RS100, Na CMC, sodium alginate, PVPK90, and HPC. For 15 minutes, these components were thoroughly combined in a polybag. From there, 100 mg of the placebo mixture was precisely weighed and added to a volumetric flask with a 100-ml capacity. 50

ml of 0.1H HCL were then added, shaken thoroughly, and then held for 60 minutes to undergo sonication. With 0.1N HCL, the residual amount was brought to 100 ml and thoroughly smashed. The resulting solution was then centrifuged at 3500 rpm for 5 minutes. A 100-ml volumetric flask was filled with 0.1 N HCL to a capacity of 100 ml using 2 ml of the supernatant solution that had been pipetted out and transferred. It was examined using a UV spectrophotometer at 234 nm. Six replicates of the identical procedure were performed. The placebo sample showed the absorbance values of the 0.0006±0.0003. The placebo shows negligible absorbance values. By the above results it was concluded that there is negligible placebo interference with NA absorbance at 234nm.

Estimation of nimodipine from dissolution of NDMF bilayered tablets to be formulated:

The individual nimodipine tablets were analyzed at 239 nm, however when the NDMF pills' nimodipine and metformin were analyzed at their respective wavelengths, interference between the two substances was evident. The overlay spectrum of nimodipine and metformin revealed that there was minimal interference at 283 nm and maximal interference at 239 nm and 234 nm. Therefore, 263nm was chosen as the maximal wavelength for the analysis of the Nimodipine samples produced from the dissolving experiments of NDMF tablets. The interference of metformin on nimodipine absorbance at 263 nm was less pronounced.

HPLC method for estimation of metformin from dissolution of NDMF tablets to be formulated

Nimodipine may interact with the absorbance of metformin, making it impossible to evaluate metformin using a UV spectrophotometer. Therefore, Metformin from NDMF pills was analyzed using the HPLC technique.

Preparation of buffer (pH 3.0):

Transferred 6.0g of sodium dihydrogen phosphate anhydrous in a suitable container containing 1000ml of Mille water, dissolved and mixed well. The pH of the above solution was adjusted to 3.0 with ortho phosphoric acid. To this 0.36g of sodium salt1-octanesulfonic acid was added and mixed well. The solution was subjected to sonication for 5 minutes for complete dissolving and then filtered through 0.45µ Pall Pharma lab nylon66 membrane filter. Mobile Phase A was prepared using Buffer (pH3.0) and methanol were mixed in the ratio of 80:20v/v respectively. Mobile Phase B was prepared using Buffer (pH 3.0) and acetonitrile were mixed in the ratio 20:80v/v

respectively. Both the mobile phases were degassed in a sonicator for about 10 minutes. Diluent is prepared using Buffer (pH 3.0) and methanol were mixed in the ratio 90:10v/v respectively.

Metformin Standard Preparation:

55mg of Metformin working standard was weighed accurately into 100ml volumetric flask. It was dissolved and diluted to volume with 0.1N HCL. 5ml of the above solution was diluted to 50ml with diluent. The collected dissolution sample was filtered through 0.45µ membrane filter by discarding the first 5ml. 3ml of the filtered sample was diluted to 25ml in a volumetric flask with diluent and mixed well. Different concentrations of nimodipine were prepared and analyzed with HPLC Technique to determine the linearity. Calibration curve of nimodipine in 0.1N HCl at 263nm

PREFORMULATION STUDIES:

Pre compression parameters:

The tablet blends were evaluated for their bulk density, tapped density, Carr's index and flow properties.

Determination of solubility of Nimodipine:

Saturation solubility studies were executed to examine the solubility of nimodipine in various solvents: 0.1N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and distilled water. These experiments were carried out under controlled conditions at 37°C. In each trial, a 100ml volume of the specific solvent was placed within a stoppered conical flask with a capacity of 250ml. Gradual addition of nimodipine was undertaken until a state of supersaturation was reached. Subsequently, a segment of the resultant saturated solution was collected, and to facilitate analysis, it was centrifuged at 3500rpm for 5 minutes. After suitable dilution, the samples were subjected to UV spectroscopy at a wavelength of 239nm. Amount (mg) = Equivalent wt. of drug×100×100/Assay value× (100-water by KF)

Dose calculation of active ingredients:

Amount of the pure drug to be taken is given by the formula (1);

$$\boldsymbol{Amount(mg)} = \{\boldsymbol{Equivalent\ weight\ of\ drug} \times \mathbf{100} \div \boldsymbol{Assay\ value} \times (\mathbf{100} - \boldsymbol{water\ by\ KF})\} \times \mathbf{100}$$

PREPARATION OF TABLETS:

Preparation of nimodipine tablets:

The formulation details for the tablet can be found in **Table 1**. Weighed amounts of the ingredients were passed through a sieve with a mesh size of 40. After sieving these materials were thoroughly mixed together in a bag for about 30 minutes to ensure proper blending. To create the granulating fluid the surfactants SLS and polysorbate 80 were dissolved separately in hot water respectively. This solution was used to moisten the blend

during the granulation process. The wet mass was then granulated using an RMG granulator. The resulting granules were dried in a Retsch dryer at a temperature of 60°C for approximately 60 minutes until the loss on drying (%LOD) decreased to below 3%. Once dried the granules were sieved through a screen with a mesh size of 40. Then subjected to lubrication. Lubrication was achieved by mixing the granules with a lubricant that had previously undergone sieving, with a mesh size of 60. This mixing process took place in a bag for around 15 minutes. Following that we assessed the flow properties of the lubricated granules. The final step involved compressing these lubricated granules using a tablet compression machine (CADMACH) equipped with shaped punches measuring 7mm in diameter.

Table 1: Composition of IR layer of nimodipine tablets

S. No.	Ingredients	Quantity Per Tablet in g								
		ND 1	ND 2	ND 3	ND 4	ND 5	ND 6	ND 7	ND 8	ND 9
1	Nimodipine	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
2	Crospovidone	0	0.00603	0.00603	0.00603	0.00603	0.00603	0.00603	0.00603	0.00603
3	Calcium carbonate	0.025	0.025	0.025	0.025	0	0.025	0	0	0
4	Aerosil	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001	0.001
5	Lactose MHF	0.03115	0.03115	0.03115	0.03115	0.03115	0.03115	0.03115	0.03115	0.03105
6	MCC PH 101	0.05145	0.0452	0.044575	0.044575	0.074575	0.049575	0.049575	0.049825	0.046075
7	Magnesium Stearate	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005	0.0005
8	Sodium bicarbonate	0.005	0.005	0.005	0.005	0	0	0.025	0.025	0.025
9	Polysorbate 80	0	0	0	0.000625	0.000625	0.000625	0.000625	0.000375	0.000375
10	SLS	0	0	0.000625	0	0	0	0	0	0
11	HPC-L	0	0	0	0	0	0	0	0	0.00370
12	Sunset yellow	0.0003115	0.0003115	0.0003115	0.0003115	0.0003115	0.0003115	0.0003115	0.0003115	0.0003115
13	Purified Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total wt of Tablet	0.14441	0.1441915	0.1441915	0.1441915	0.1441915	0.1441915	0.1441915	0.1441915	0.1440415

Preparation of Metformin tablets:

Refer to **Table 2** for the tablet composition specifics. The drug and polymer, previously sieved using a 40-mesh screen, were meticulously mixed inside a polybag for a duration of 20 minutes. The blended mixture was dampened with a granulating solution consisting of a combination of water and IPA in a 1:9 ratio. The resulting wet mass was then passed through a 24-mesh screen to ensure uniform particle size. Subsequently, the damp granules underwent drying in a tray dryer set at 50°C for approximately 50 minutes, until the percentage of loss on drying (% LOD) reduced to below 2%. Following drying, the granules were sieved again through a 30-mesh screen. The sodium bicarbonate and dry granules were then mixed together for ten minutes inside a polybag. Talc that had previously been sieved through a 60-mesh

screen was added after that, and thorough mixing was completed over the course of 10 minutes. To determine the quality of the lubricated granules, their flow characteristics were evaluated. Finally, a 16-station tablet compression machine (CADMACH) outfitted with 13.1mm round concave punches was used to crush the lubricated granules.

Table 2: Composition of metformin CR tablets

S. No.	INGREDIENTS	QUANTITY PER TABLET IN G										
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
1	METFORMIN	0.39	0.39	0.39	0.3859	0.39	0.39	0.39	390	0.39	0.39	0.39
2	HPMC K 100M	0.245	0.245	0.245	0.245	0.245	0.245	0.245	0.245	0.245	0.15	0.35
3	SBC	0.075	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
4	AEROSIL	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.003
6	EUDRAGIT RSPO	0.03	0.03	-		-	-	-	-	-	30	30
7	EUDRAGIT RLPO	-	-	0.03		-	-	-	-	-	-	-
8	EUDRAGIT RS100	-	-		0.03	-	-	-	-	-	-	-
8	Na CMC	-	-	-	-	0.03	-	-	-	-	-	-
9	SODIUM ALGINATE	-	-	-	-		0.03	-	-	-	-	-
10	HPC KLUCEL HF	-	-	-	-	-	-	0.03	-	-	-	-
11	PVPK 90	-	-	-	-	-	-	-	0.03	-	-	-
12	ETHYL CELLULOSE	-	-	-	-	-	-	-	-	0.03	-	-
13	TALC	0.0031	0.0031	0.0031	0.0031	0.0031	0.0031	0.0031	0.0031	0.0031	0.0031	0.0031
14	IPA	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
15	PURIFIED WATER	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
	TOTAL WEIGHT	0.7461	0.7711	0.7711	0.7711	0.7711	0.7711	0.7711	0.7711	0.7711	0.6761	0.8761

Preparation of bilayer tablets of NDMF:

A bilayered tablet compression machine was used to compress the bilayered tablets of nimodipine and metformin (NDMF) utilizing 13.1mm round concave punches.

The nicotinic acid granules were positioned first and pre-compressed to a softness of about 4-5KP. The aspirin granules were then added and compacted until they reached a final hardness of about 12- 14 KP. The final NDMF tablets' post compressional parameters were carried out. Composition of optimized nimodipine and metformin layers in **Table 3 and 4**.

Table 3: Composition of optimized Niomodipine layer in NDMF tablets

S. No.	INGREDIENTS	QUANTITY PER TABLET in G
1	Nimodipine	0.03
2	Cross povidone	0.00603
3	Aerosil	0.001
4	LMFL	0.03115
5	Microcrystalline cellulose PH101	0.046050
6	Sodium bicarbonate	0.025
7	Polysorbate 80	0.000374
8	HPC-L	0.00370
9	Magnesium stearate	0.0005
10	Sunset yellow (0.25%)	0.0003115
11	Purified water	Quantity Sufficient
	Total weight	0.114115

Table 4: Composition of optimized metformin layer in NDMF tablets

S. No.	INGREDIENTS	QUANTITY PER TABLET IN G
1	Metformin	0.3748
2	HPMC K100M	0.245
3	SBC	0.1
4	Aerosil	3
5	Eudragit RSPO	0.003
6	Talc	0.0031
7	Iso propyl alcohol	Quantity Sufficient
8	Distilled water	Quantity Sufficient
	Total weight	0.7559

FLOW PROPERTIES OF LUBRICATED GRANULES:

The flow characteristics of lubricated granules, derived from the wet granulation process involving nimodipine and metformin, are examined. This assessment includes the analysis of flow-related attributes such as bulk density, tapped density, compressibility index, Hausner's ratio, and angle of repose. These evaluations provide insights into the granules' flow behavior and properties, which are essential in pharmaceutical formulation and processing. Different excipients are utilized during the wet granulation process, contributing to the overall quality and performance of the final product.

EVALUATION OF TABLETS:

The hardness, weight, thickness, friability, and disintegration time for all the tablets were tested, and the drug content in all the batches was measured. Dissolution studies were done for all the formulations too.

Evaluation parameters for Floating Tablets:

Floating lag time (FLT):

The Metformin tablet is located into a beaker with 250 ml of 0.1N HCl solution, and timed how long it took for the pill to float and stay up. They recorded this time as FLT.

Total floating time (TFT):

The duration (in hours) for which the Metformin tablet maintains buoyancy was observed and registered as TFT.

Assessment of the swelling index of Metformin tablets:

The tablet, initially weighed (W1), was positioned within a USP apparatus type-I, submerged in a container holding 900 ml of 0.1N HCl, and kept at a temperature of 37±0.20°C. At predetermined intervals (up to 8 hours with 1-hour intervals), the tablets were taken out from the basket and positioned on absorbent paper to eliminate excess liquid **(as shown in Figure 1)**. Following this, the tablet's weight was measured again (W2). This process was replicated three times for each formulation. The swelling index was computed using the subsequent formula:

$$\text{Swelling index} = W2 - W1/W1 \times 100$$

Figure 1: The expansion behavior exhibited by Metformin tablets

Determination of drug content of nimodipine tablets:

The tablet of ten nimodipine were precisely weighed and subsequently finely ground using a clean mortar and pestle. 25mg of the drug was measured (W_s) and then introduced into a 100ml volumetric flask with 0.05l of methanol followed by sonication for 5 minutes at a temperature of 27°C. The solution's final volume was adjusted to 0.01l using methanol (V4). A 4ml portion (V5) from this solution was then transferred to another 100ml volumetric flask and brought to a final volume of 0.1l (V6) using 0.1N HCl (pH 1.2). The flask was agitated for 5 minutes, after which the sample was subjected to drug content analysis at with the help of a UV Spectrophotometer at 239nm.

Determination of drug content of Metformin tablets:

The weighed 10 tablets of Metformin and crushed them up in a mortar and pestle. Then I weighed out the powder, which was 100mg. I put it in a clean and dry 100ml volumetric flask, added 50ml of 0.1N HCl, and mixed it all up for 10 minutes. After that, I used sonication for 4 hours, adjusted the volume to 0.0ll with 0.1N HCl, and shook it for 5 minutes. Then I centrifuged it at 3000rpm for 10 minutes, filtered it with a 0.45µm Whatman filter paper, and took 2ml of the filtered solution for transfer into another 100ml volumetric flask. I brought the volume up to 100ml with 0.1N HCl, shook it for 5 minutes, and used a UV Spectrophotometer to examine the drug content at 234nm.

IN VITRO DRUG RELEASE STUDIES:

In vitro drug release studies of nimodipine tablets:

In accordance with the guidelines established by the United States Pharmacopeia (USP), the in-vitro drug release investigations for nimodipine tablets were executed. Prior to the commencement of the study, both the dissolution methodology and the equipment employed were subjected to validation procedures. The dissolution process for all tablet batches was conducted utilizing the LABINDIA DISSO 2000 apparatus, featuring an automatic sampler. USP Apparatus-II Paddle-type setup were the dissolution is performed with 0.1N HCl (with 6.8pH phosphate buffer) as the dissolution media for the dissolution. The total volume was 900ml.

To ensure the dissolution medium was free of gases, it was subjected to degassing by placing the dissolution vessel with the medium in a water bath set at 37±20C. The rpm of paddle's was configured at 75rpm, while the temperature was rigorously maintained at 37±0.50C. During the dissolution process, 10ml of the sample was withdrawn at specific time intervals (5, 10, 15, 20, 30, and 45 minutes), with a rinsing volume of 3ml and a replacement volume of 10ml. The pooled samples collected were subsequently analyzed at a wavelength of 239nm using a UV-Spectrophotometer.

In vitro drug release studies of metformin tablets:

All the formulated Metformin tablets were subjected to in vitro drug release assessments. The experimental procedure and equipment employed had been previously validated. The tablets were securely positioned within sinkers and introduced into six separate vessels of the USP Type-II dissolution apparatus **(depicted in Figure 2)**. A total of 900ml of previously degassed 0.1N HCl solution was employed as the dissolving medium. The paddle was set to rotate at 100 revolutions per minute, while the temperature was precisely maintained at 37.50°C. For each 10ml sampling, a fresh batch of the dissolution medium was replenished. Sample collection occurred at specific intervals spanning 1, 3, 6, 9, and 20 hours. These samples were gathered and combined to create pooled samples, subsequently subjected to examination using a UV-Spectrometer set at 234nm.

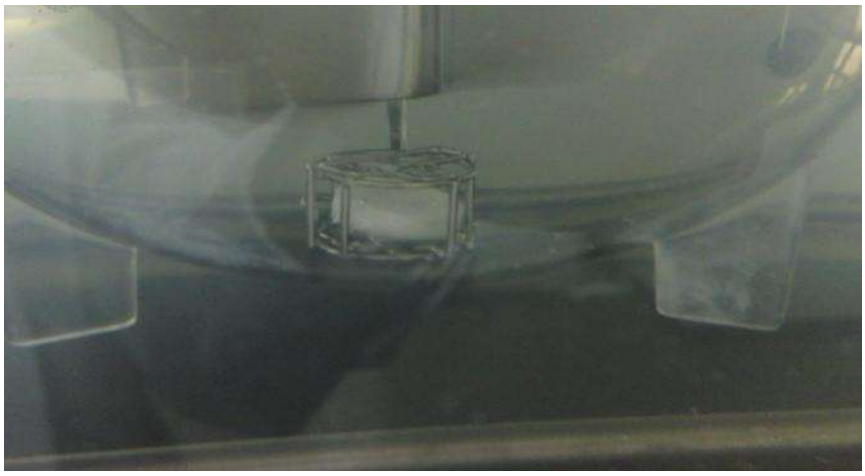

Figure 2: In vitro drug release study of nicotinic acid tablet using sinkers

In vitro drug release studies of bilayer floating tablets of NDMF:

The investigation of drug release from NDMF bilayered tablets was carried out using a USP apparatus-II paddle-type setup equipped with an automatic sampler. The tablets were securely positioned within sinkers during the experiment. A total of 900ml of 0.1N HCl solution, which had been previously degassed, was employed as the dissolution medium. The temperature was rigorously maintained at 37±0.50°C, and the paddle was set to rotate at a speed of 100 revolutions per minute. Each sampling session involved withdrawing 10ml of the solution, and an equivalent volume of the dissolution medium was replaced accordingly. The sampling intervals differed, being set at 5, 10, 15, 20, 30, and 45 minutes for the nimodipine component, and 1, 3, 6, 9, 12, and 20 hours for the metformin component. The samples collected from each interval were combined to create pooled samples for subsequent analysis. These pooled samples underwent analysis using a UV-Spectrometer, with a wavelength of 234nm for the metformin portion and 239nm for the nimodipine portion. The drug release investigations for both components were conducted using 6 units for each formulation.

Selection of optimized batch of Nimodipine and Metformin Tablets:

The picked out the most efficient combo of nimodipine and metformin tablets based on the similarity factor (f 2) which was calculated compared to the drug release of the already-available nimodipine tablet and the patented metformin tablet. Similarity factor is calculated between the factor % drug release of marketed tablets; Nimodipine and Metformin formulations respectively, by using the formula;

$$f_2 = 50\mathrm{X}\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5}\mathrm{X}100\right\}$$

Rt and Tt are the percentages of the drug that have dissolved at time t for the reference and test respectively, and n is the number of times they were tested. If the f2 value is over 50 (close to 100), then the drug's dissolution is considered okay.

PACKAGING:

Selected batches of NDMF were packed in 85mm HDPE bottles with an oxygen adsorbent, a molecular sieve and a desiccant containing silica gel with cotton as filler. Oxygen Adsorbent is added to prevent AS from oxidation. Molecular sieve and desiccant absorb moisture.

These are fixed with CRC caps and then sealed by using Induction Cap Sealing Machine.

Accelerated stability studies of NDMF tablets:

Accelerated stability tests on NDMF bilayered tablets were conducted for a month at 45°C and 75% RH. The NDMF tablets were contained in 85mm HDPE bottles together with an oxygen absorbent, a molecular sieve, and a desiccant made of silica gel with cotton as filler. After the stability period, the tablets were removed and tested for physical characteristics such as weight variation, thickness, hardness, %friability, disintegration time of the nimodipine layer, FLT and TFT of the metformin layer, and in vitro drug release tests. For the initial sample and the stability sample, the similarity factor was determined.

RESULTS AND DISCUSSION

The oral absorption characteristics of nimodipine, classified as a BCS Class-II medication, primarily depend on its solubility. In this study, a variety of excipients were employed to enhance the dissolution rate of nimodipine. Hyperglycemia is treated with elevated metformin doses. Nimodipine's rapid-release formulation contributes to blood pressure reduction. To mitigate metformin's adverse effects, diverse approaches like sustained-release formulations have been devised. Given metformin's predominant absorption in the stomach and upper small intestine, controlled-release tablets were formulated in this research to achieve prolonged drug release and enhance oral bioavailability. The investigation also delved into the impact of various polymers on drug release rates, involving the combination of HPMC K100 with other polymer agents.

Table 5: Standard graph of nimodipine in 6.8 pH Phosphate buffer at 239nm

Concentration (µg/ml)	Absorbance at 239nm
0	0
5	0.1998±0.0003
10	0.3995±0.0004
15	0.5930±0.0003
20	0.7837±0.0002
25	0.9888±0.0003
R^2	0.9999

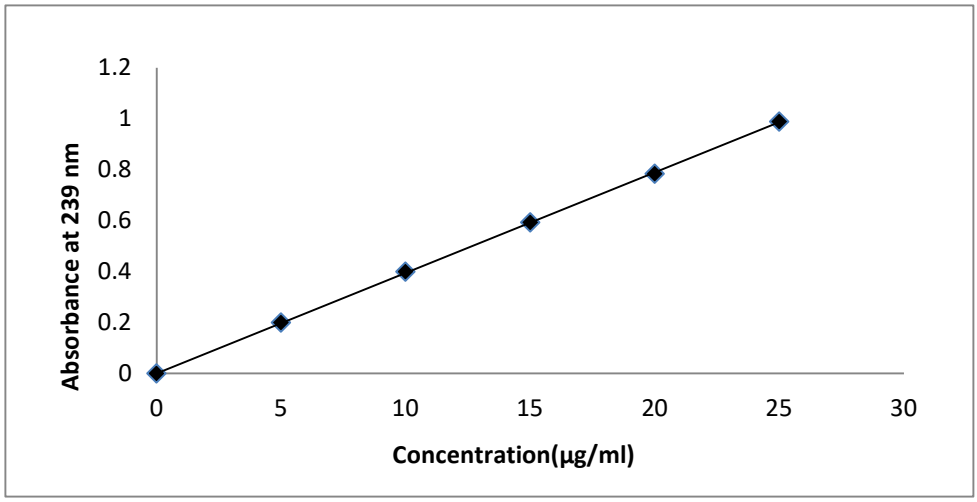

Figure 3: Calibration curve of nimodipine in 6.8pH phosphate buffer at 239nm

Table 6: Standard graph of nimodipine in 0.1N HCl at 239nm

concentration (µg/ml)	Absorbance at 239nm
0	0.0000
5	0.1851±0.0002
10	0.3759±0.0004
15	0.5615±0.0002
20	0.7553±0.0003
25	0.9464±0.0002
R^2	0.999

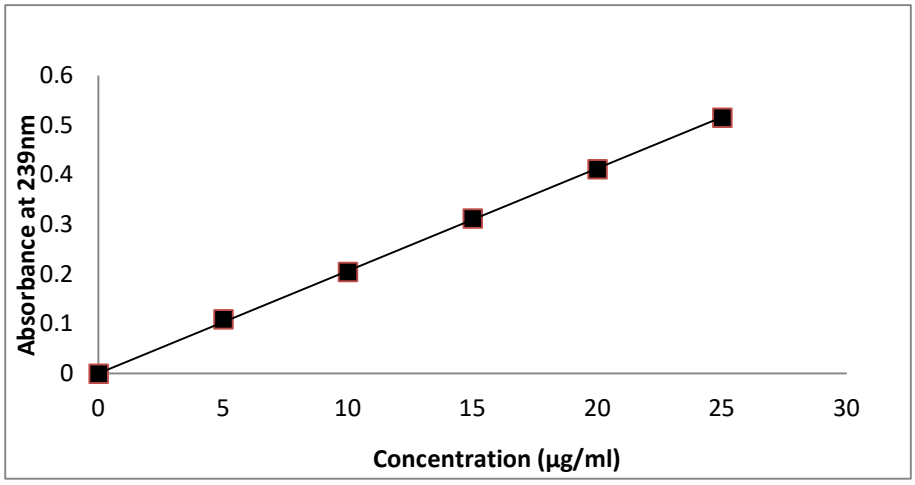

Figure 4: Calibration curve of nimodipine in 0.1N HCl at 239nm

Table 7: Standard graph of metformin in 0.1N HCl at 234nm

Concentration (µg/ml)	Absorbance at 233nm
0	0.0000
5	0.2439±0.0002
10	0.4235±0.0003
15	0.6458±0.0001
20	0.8355±0.0002
25	1.0684±0.0003
R^2	0.998

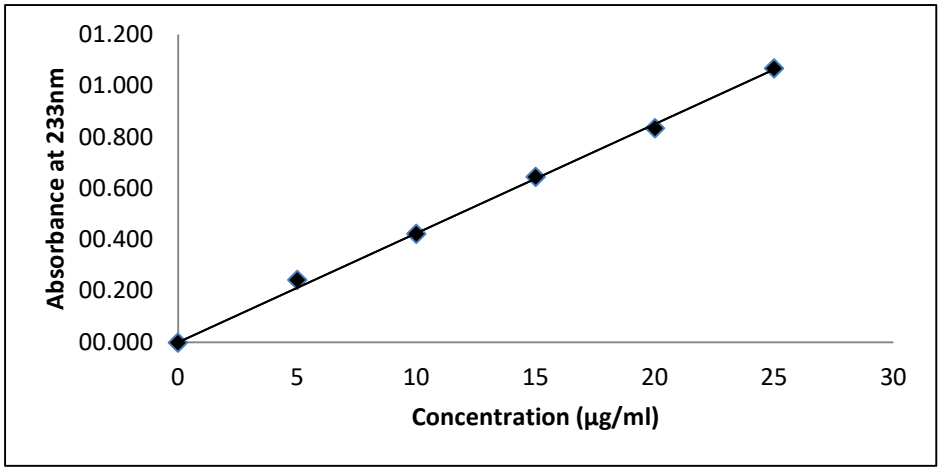

Figure 5: Calibration curve of metformin in 0.1N HCl at 234nm

Table 8: Absorbance of different concentrations of nimodipine at different wavelengths

concentration (µg/ml)	Absorbance Values		
	239nm	233nm	283nm
0	0.0000	0.0000	0.0000
5	0.1808±0.0002	0.1861±0.0003	0.1098±0.0002
10	0.3526±0.0001	0.3739±0.0002	0.2050±0.0002
15	0.5437±0.0003	0.5605±0.0001	0.3122±0.0001
20	0.7171±0.0002	0.7543±0.0003	0.4114±0.0003
25	0.8931±0.0001	0.9454±0.0002	0.5155±0.0002
R2	0.9999	1.0000	0.9999

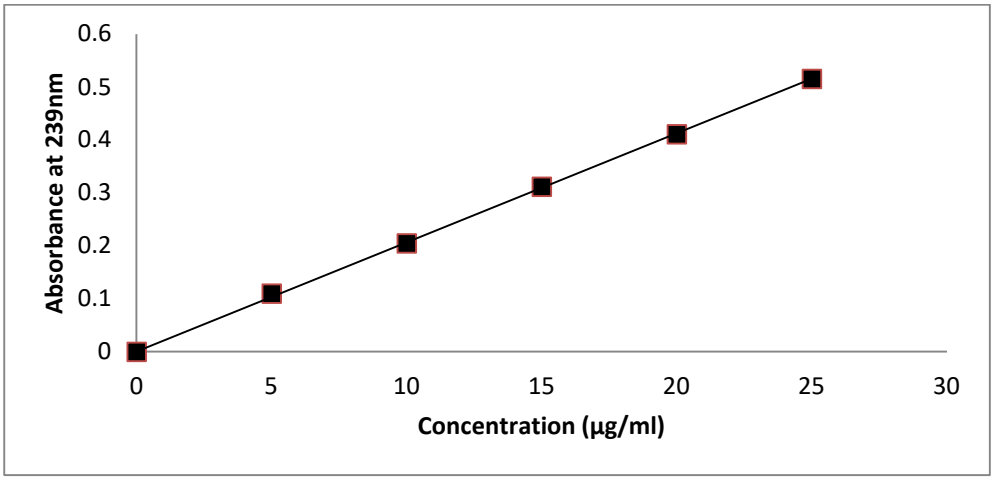

Figure 6: Calibration curve of nimodipine in 0.1N HCl at 239nm

Table 9: Standard graph of metformin in 0.1N HCl at 234nm.

Concentration (µg/ml)	Standard Area
0	0.0000000
5	1058365.5
10	2116731.0
15	3175096.5
20	4233462.0
25	5291827.5
R^2	1.0000

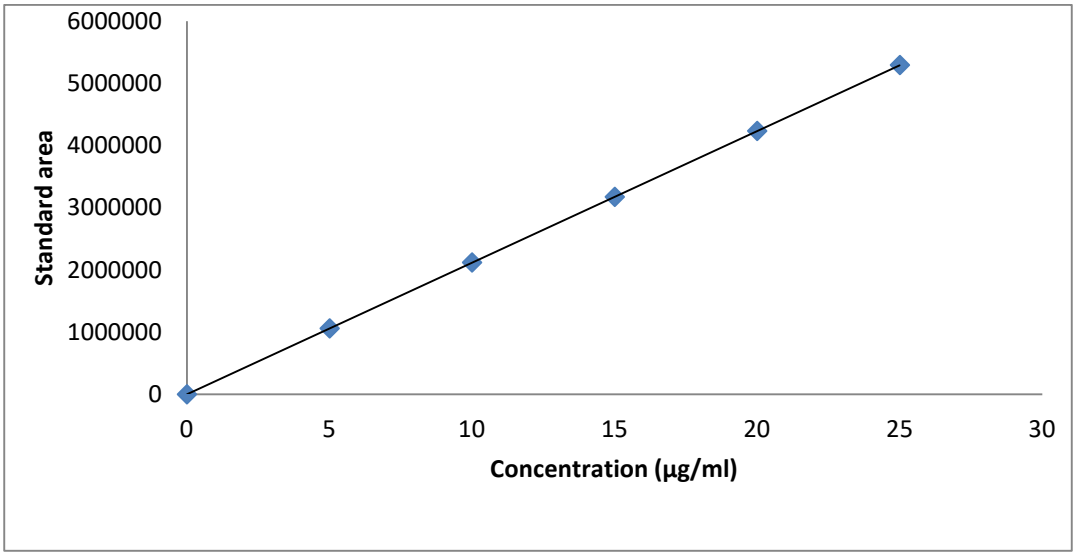

Figure 7: Calibration curve of metformin in 0.1N HCl at 234nm

Drug excipient compatibility studies:

The FTIR spectra analysis of nimodipine and its blends revealed indistinguishable profiles. The main absorption peaks in nimodipine **(Figure 8)** were also evident in metformine and formulations containing nimodipine, specifically at 3403.92 cm^-1 (alcoholic O-H stretch), 3058.20 cm^-1 (C-H stretch aromatic), 1662.24 cm^-1 (carbonyl C=O stretch), 1594 cm^-1 (amine N-H bend), and 692.03 cm^-1 (C-F). This observation from FTIR studies indicated the absence of interactions between the drug and excipients. The FTIR data for pure metformin is shown in **Figure 9**. Comparative analysis demonstrated that the peaks in physical mixtures perfectly aligned with those of the pure drug, displaying a correlation coefficient exceeding 0.9, as depicted in **Figure 10 and Figure 11**. Thus, the FTIR investigations affirm the absence of drug-excipient interactions.

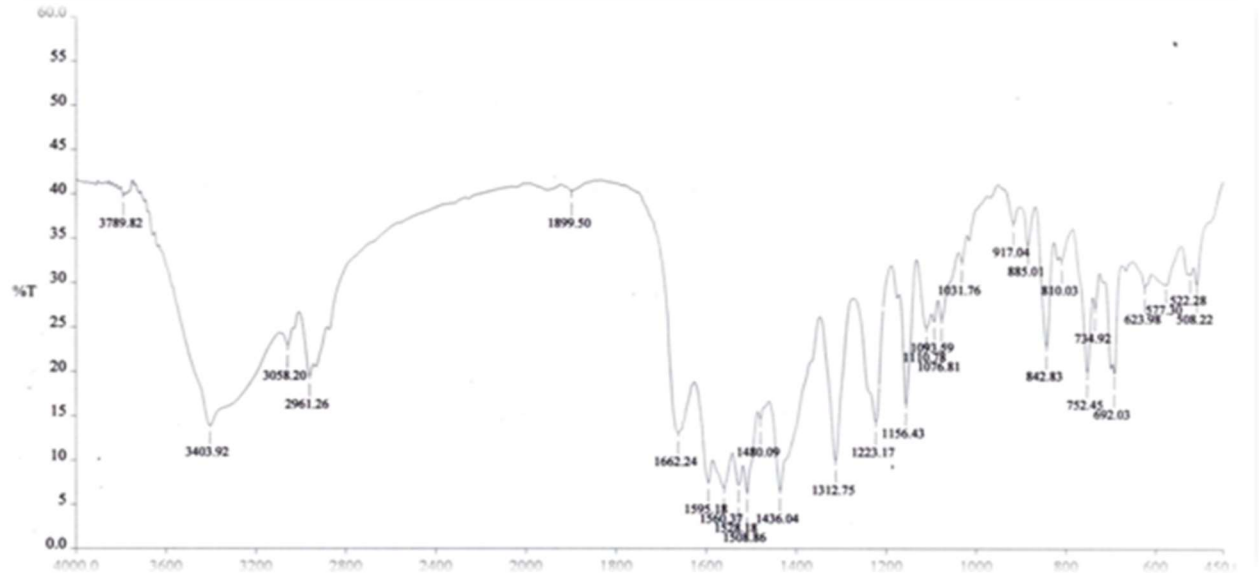

Figure 8: FTIR spectra of Nimodipine

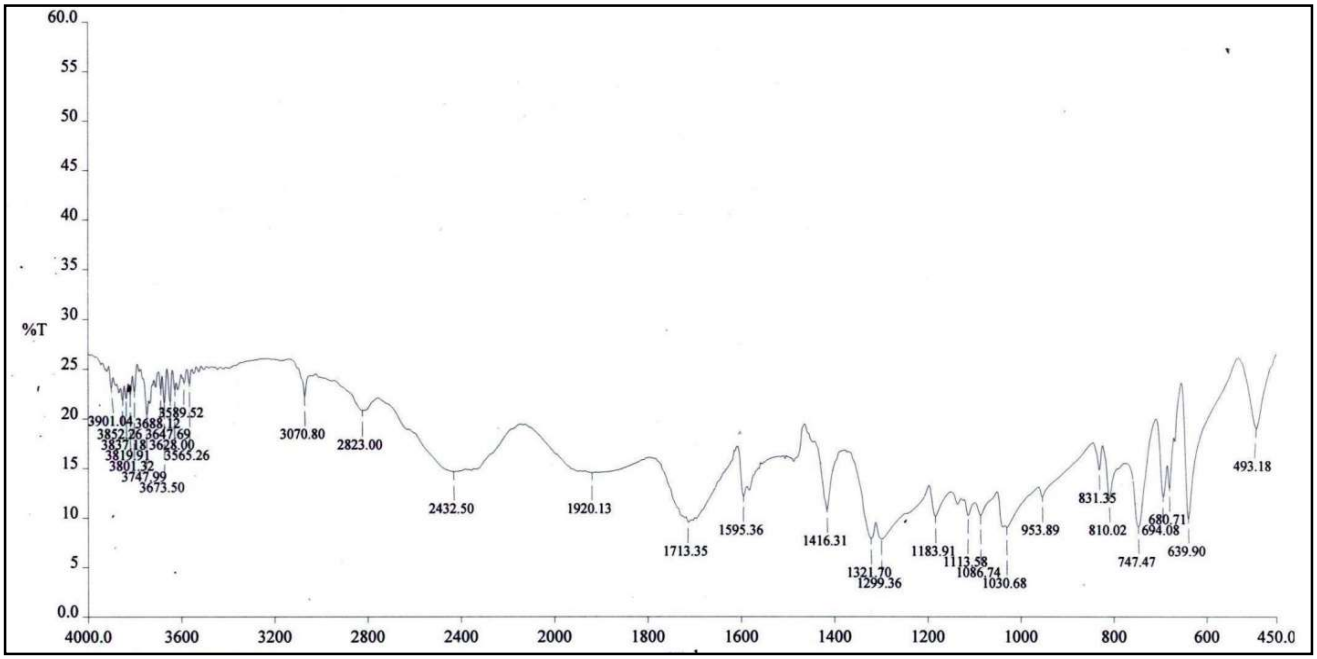

Figure 9: FTIR spectra of metformin

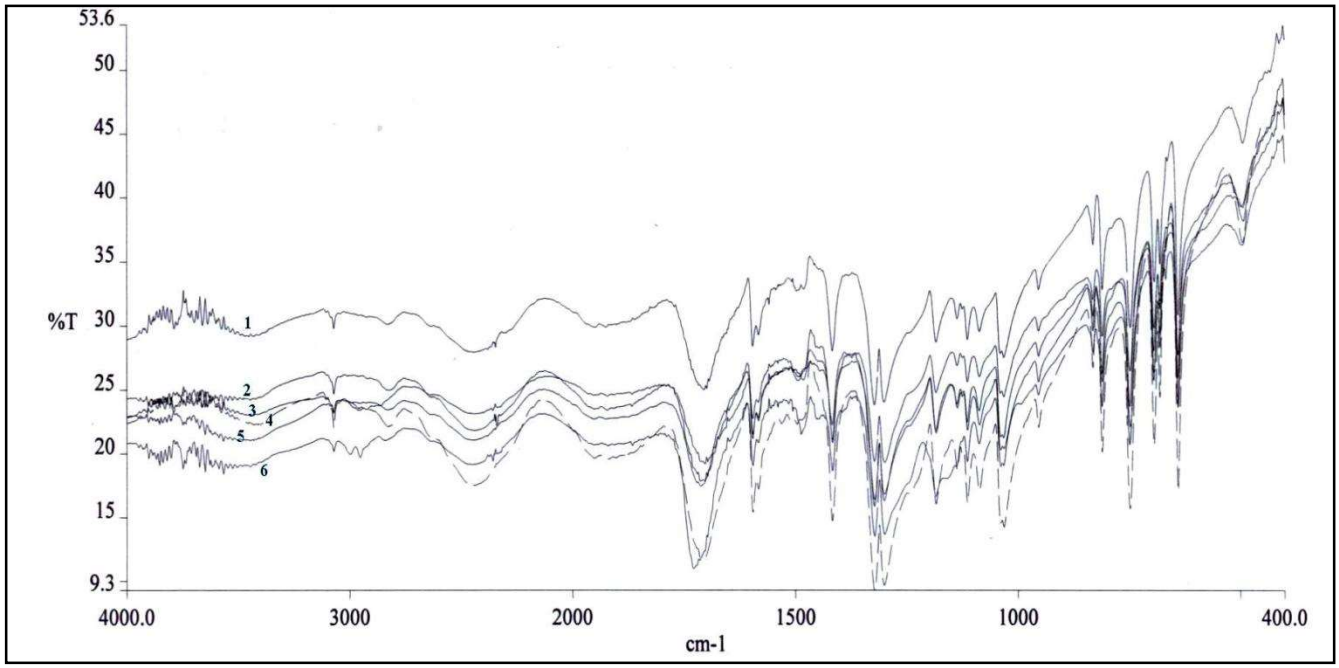

Figure 10: FTIR spectra of physical mixtures of polymers containing metformin1- MF; 2-MF+Eudragit RS PO; 3-MF+HPMC; 4- MF+PVPK90; 5-MF+Eudragit RS 100; 6-MF+Eudragit RLPO

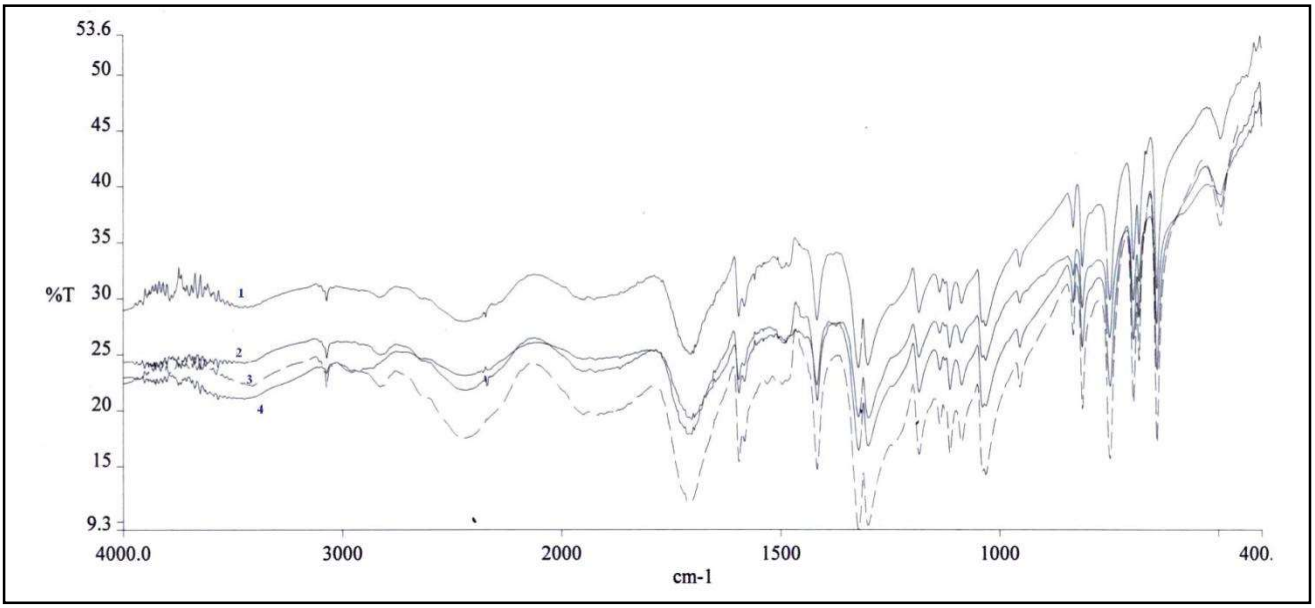

Figure 11: FTIR spectra of physical mixtures containing metformin 1-Pure MF; 2-MF+SCMC; 3-MF+HPC; 4-MF+Sodium alginate

Solubility study:

According to **Table 10**, Nimodipine's solubility was pH-dependent and increased in an alkaline environment. Therefore, our investigation showed that adding alkalizing agents to the nimodipine formulation speeds up nimodipine dissolving.

Table 10: Solubility of nimodipine in different buffers

S. No	Medium	Solubility (mg/ml)
1.	0.1 N HCl	0.0598
2.	0.001 N HCl	0.219
3.	pH 4.5 Acetate Buffer	0.0598
4.	Purified Water	3.0
5.	pH 6.8 phosphate buffer	0.6597
6.	pH 7.5 phosphate buffer	1.12
7.	pH 2.1 SGF	0.81
8.	pH 5 Simulated Intestinal Fluid	0.8498

Flow properties of pure drugs:

The preformulation assessment of the pure Niomodipine drug revealed unfavorable flow characteristics **(Table 11)**, making it unsuitable for direct compression in formulation. To address this, Niomodipine granules were created using the wet granulation approach.In contrast, the pure Metformin drug exhibited favorable flow properties **(Table 12)**, evident from the Carr's index value (15.63) and angle of repose (28.52). This indicated its suitability for direct compression tablet formulation due to its smooth flow properties. Nevertheless, metformin floating tablets were developed via the wet granulation method, enhancing granule porosity and conferring buoyancy to the tablets.

Table 11: Pre compression properties of nimodipine

S. No.	Parameter	Observation
1	Polymorphic State	Amorphous
2	Bulk Density (g/ml)	0.307
3	Tapped Density (g/ml)	0.553
4	Carr's Index (%)	44.38
5	Hausner's Ratio	1.797
6	Angle of Repose (Ɵ)	64.00
7	Result	Poor

Table 12: Pre compression properties of metformin

S. No.	PARAMETER	OBSERVATION
1	Polymorphic State	Crystalline
2	Bulk Density (g/ml)	0.706
3	Tapped Density (g/ml)	0.837
4	Carr's Index (%)	15.64
5	Hausnner's Ratio	1.186
6	Angle of Repose (Ɵ)	28.53
7	Result	Good Flow

Table 13: Pre compression Parameters of lubricated granules of nimodipine

Formulation Code	Angle of Repose (Θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio	%LOD
ND1	28.01	0.507	0.687	26.20	1.355	2.09
ND2	28.26	0.521	0.622	21.31	1.271	2.98
ND3	27.76	0.546	0.694	21.33	1.271	2.73
ND4	26.79	0.454	0.547	17.17	1.204	2.16
ND5	27.03	0.503	0.629	20.03	1.250	2.10
ND6	26.79	0.506	0.634	20.19	1.252	2.93
ND7	27.03	0.502	0.609	17.57	1.213	2.83
ND8	27.76	0.526	0.676	22.25	1.285	2.96
ND9	27.27	0.501	0.615	18.54	1.227	2.63
ND10	27.03	0.500	0.627	20.25	1.254	2.86
ND11	27.03	0.507	0.625	18.88	1.232	2.92

Table 14: Pre compression Parameters of lubricated granules of metformin

Formulation Code	Angle of Repose (Θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio	%LOD
F1	32.00	0.388	0.556	28.65	1.432	1.739
F2	33.33	0.350	0.503	33.05	1.437	1.889
F3	33.70	0.355	0.504	29.67	1.419	1.9329
F4	33.33	0.333	0.479	28.70	1.438	1.828
F5	32.64	0.336	0.495	31.55	1.473	1.798
F6	33.68	0.349	0.484	27.82	1.386	1.873
F7	33.68	0.343	0.483	28.63	1.408	1.924
F8	33.32	0.349	0.490	28.70	1.404	1.903
F9	34.05	0.351	0.502	29.61	1.430	1.766
F10	33.36	0.322	0.468	31.12	1.453	1.968
F11	33.68	0.323	0.468	30.90	1.448	1.697

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