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FORMULATION AND EVALUATION OF MATRIX TABLET LOADED LYOPHILIZED BENIDIPINE

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ABSTRACT

An antihypertensive drug, Benidipine (BND) is Biopharmaceutical Classification System Class-II drug having low solubility and high permeability and has lower bioavailability. The present study describes the preparation of matrix tablet from lyophilized BND nanoparticles as lyophilization technique is used in order to improve the dissolution and oral bioavailability of the drugs with poor solubility and high permeability, matrix tablet was formulated to achieve extended drug release and to study its drug release pattern as well. BND has mean half-life 5.3 hr and requires frequent dosing every 5-6 hr to maintain optimal relive and used orally in the treatment of hypertension and angina pectoris, but this frequent administration produces side effects like dizziness and headache. So in present study we have achieved extended drug release for time up to 25 hr for treatment of hypertension, for continuous 24 hr control of blood pressure (BP), by using polymers HPMC K4, chitosan, MCC, magnesium stearate, lactose and talc in order to prepare the suitable formulation. Matrix tablets of lyophilized BND nanoparticles was formulated using 3^2 factorial design in order to study the effect of independent variables X_1 and X_2 (i.e. amount of HPMC K4 and Chitosan respectively) on dependent variable (i.e. % drug release in 10 hr (Q_{10}) and time require for 80% drug release (T_{80})) to evaluate extended drug release. The tablets were prepared by direct compression method. *In-vitro* drug release of different formulations was carried out under stimulated gastric and intestinal condition to achieve optimized drug release. Optimized batch F5 has achieved 99% drug release in 25 hr. The physiochemical characterizations of all prepared formulations

were found to be satisfactory. Fourier transform infrared spectroscopy (FTIR) study of optimized F5 batch was performed to study any interaction of BND with polymer.

Keywords: Benidipine, Bioavailability, lyophilization, hypertension, direct compression method, Matrix Tablet

INTRODUCTION

In present decade conventional drug formulations which are used in treatment of chronic disorders, has to be administered frequently in multiple dosage regimens, which sometimes creates various undesirable effects. So, in order to avoid the effects associated with multiple dosing, BND extended release solid unit dosage forms as tablets were developed using Lyophilization from nanosuspension. The main advantages of this type drug delivery is they shows better patient compliance, maintain uniform drug therapeutic level and increase the safety margin for high potency therapeutic agents by reducing dose as well as their side effects. However, bioavailability of BND is limited by its poor water solubility following oral administration. Therefore, solubilization technique were applied and reported to enhance the aqueous solubility of BND. For improving the solubility and dissolution rate of the BND in water, formation of nanosuspension by Media milling were carried out. Solidification technique like Lyophilization, Spray drying is more suitable for products that can withstand higher temperature, and thus may not be feasible for heat labile products **[1, 2, 3]**. Amongst all these techniques, lyophilization is used predominantly for nanosuspension solidification, as it offers several advantages including, production of high value products without excessive damage, suitable for drying of heat labile product, enhanced stability on storage and easy reconstituability prior to use. It is reported that physical and chemical interactions take place faster in liquid form as compared to solid form **[4]**. An optimized batch of nanosuspension was lyophilized to maintain the stability of nanosuspension.

Lyophilization is defined as a stabilizing process in which the samples is frozen by a reduction of the solvent content by sublimation and then by desorption to values that will no longer allow biological growth or chemical reactions **[5]**. A shelf life of pharmaceutical products and foods has been demanded to extend a period of time. Lyophilization is also importance to maintain their storage characteristics. The most key factor to decline the product quality is water included in formulation. Therefore, an appropriate drying method should be used to

remove water from the formulated drug products. The interest in freeze-drying known as Lyophilization drastically increased with the growing numbers of antibiotics and other sensitive pharmaceuticals. Lyophilization has evolved to a well-established technology for preservation of biopharmaceuticals as well pharmaceutical products **[6]**. This is process normally consists of three stages: (1) freezing stage, (2) primary drying stage, and (3) secondary drying stage.

The main object of present study is to formulate extended release formulations from lyophilized powder to get a more uniform plasma drug profile. Now a day's extended release drug delivery playing an important role by avoiding frequent administration of drug compared to conventional formulation. Out of among all different extended release system, matrix system is a simple and novel method for modulating drug. The term matrix indicates a three dimensional network composed of drugs, polymers and different excipients. Because of simplicity; ease in manufacturing and low costs, matrix preparation has become a popular approach **[7, 8]**. Once in a day, dosing of extended drug delivery systems ensures that patients should not skip their medications and this enhances their compliance to medication. BND is dihydropyridine derivative Ca_2^+ channel antagonists, which are widely used as anti-hypertensive or anti-anginal agents by preventing the rapid vasodilatation that produces a reflex increase in sympathetic nerve activity; it results in the cardiac discomfort leading to coronary artery disease **[9, 10]**. The oral administration of BND is rapidly absorbed and shows narrow therapeutic index. The half life of BND is 5.3 hrs and its bioavailability is lower at 23-30% therefore it requires frequent dosing. Conventional tablets should have been given 2-3 times a day. Developing a dosage form will produce an extended formulation and reduce frequent dosing. Hence in this present work an extended release matrix tablet of BND has been formulated from lyophilized BND nanoparticles to increase duration of drug release by using various polymers. By formulating matrix tablets of lyophilized BND nanoparticles first pass metabolism can be avoided and it produces prolong action. The use of polymers to control the release of drugs has become important in the formulation of pharmaceuticals. In this present research we have taken the excipients like HPMC K4M, Spray Dried Lactose, Talc, and Magnesium Stearate for preparing extended release matrix tablet of lyophilized

BND nanoparticles. We have formulated a 150 mg tablet containing 8 mg of BND once daily tablet for extending drug release in spite of taking 2- 4 mg of tablet for 2 to 3 times daily, as frequent administration of drug causes side effects like headache, dizziness, palpitation, vertigo *etc* to the patient. Hypertensive patients have been treated orally with maximum dose of 8 mg BND, causes reduced blood pressure and this is maintained till 24 h, which indicate that BND has long-lasting pharmacological activity **[11, 12]**. Developed formulation will produce an extended formulation and reduce frequent dosing. Matrix tablets of lyophilized BND nanoparticles were formulated by direct compression method.

MATERIALS AND METHODS

Materials: BND was a gift from Prayosha Healthcare Pvt. Ltd. (Ankleshwar, India). HPMC K4M, Spray Dried Lactose, Talc, Magnesium Stearate, used of analytical grade was gifted from Prachin Chemical (Ahmedabad, Gujarat).

Method:

Lyophilization: BND nanosuspension was formulated using media milling technique. For freeze drying cryoprotectant, mannitol (1% w/v) was added to BND nanosuspension and then nanosuspension was frozen at -30 °C for 8 h (overnight). Before starting freeze drying the condenser coil of lyophilizer was switched to get the coil temperature -80 °C. Once the desired temperature was obtained in lyophilizer coil, glass flask containing nanosuspension was placed in prefrozen lyophilizer for 48 hours to yield dry nanoparticles in a powder form. Vacuum system was started to achieve 0.05 mmHg vacuum of drying chamber. After thawing Particle size, Zeta potential, solubility and in-vitro drug dissolution was analyzed for the lyophilized powder after reconstitution and the results were compared with those before lyophilization.

Characterization of lyophilized BND nanoparticles powder

Particle size and its morphology

Particle size of nanosuspension was determined using a Zetasizer (Malvern Instruments, UK). This analysis demonstrates the mean diameter of particles. Lyophilized BND nanoparticles powder was dissolved in deionised water and sonicated for 2 minutes to reduce aggregation. Solution was placed in disposable sizing cuvettes and analyzed. Two samples per batch have been analyzed, and the measurements were repeated three times for each sample. All the data observed are the mean values of three independent samples analyzed under identical production conditions.

Zeta potential

Zeta potential indicates the stability of the suspension. Zeta potential of Lyophilized BND nanoparticles was measured using Malvern Zetasizer ZS (Nano series ZS 90 UK). Samples of Lyophilized BND nanoparticles were suspended with sufficient water, then sample was directly placed into cuvette and zeta potential was measured and it is expressed in mV. The absolute value of zeta potential is about ±30 mV is sufficient to stabilize the solidified BND powder.

In - vitro dissolution

Dissolution study of Lyophilized BND nanoparticles was carried out in modified diffusion cell apparatus. The drug release from Lyophilized BND nanoparticles was determined using a dialysis tube (donor compartment) in which the known quantity of the sample was incorporated in a water-jacketed beaker containing 300 ml of 0.1N HCl (pH 1.2) at 37 ± 1°C for 30 mins. The beaker containing formulations were agitated on a magnetic stirrer. Accurately weighed Lyophilized BND nanoparticles were dispersed in dissolution medium. 5 ml aliquots were withdrawn at predetermined time intervals 0, 5, 10, 15, 20, 25 and 30 min from dissolution medium and replace with same buffer solution with equal volume of fresh 0.1N HCl (pH 1.2) to maintain sink condition. Samples withdrawal from dissolution medium were filtered through a 0.22 µm filter paper and assayed by UV visible spectrophotometer at 357nm wavelength. Dissolution for each formulation was performed in triplicates.

Procedure for formulation of BND matrix Tablet from lyophilized BND nanoparticles powder: Each matrix containing 8mg BND, were formulated by direct compression method. Composition of various formulations employing are shown in **Table 1**.

Table 1: Formulation of Lyophilized BND Matrix Tablet

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
BND	8	8	8	8	8	8	8	8	8
HPMC KM4	40	50	60	40	50	60	40	50	60
Chitosan	15	15	15	20	20	20	25	25	25
Lactose	66	56	46	61	51	41	56	46	36
MCC	15	15	15	15	15	15	15	15	15
Talc	3	3	3	3	3	3	3	3	3
Magnesium Stearate	3	3	3	3	3	3	3	3	3

Lyophilized BND nanoparticles powder and other excipients of tablets were blended in mortar with a pestle for 15min to obtain uniform mixture. After the sufficient mixing of drug and other ingredients, magnesium Stearate were added and further mixed for more 2 - 3 min. The blended powder was then compressed into 150 mg tablets on a single stroke, rotary punch tablet machine with 8mm round shaped flat punch. Weight

of tablets was kept constant (150 mg) for tablets of all batches. We have formulated batches using factorial design 3^2 to optimize matrix tablet of lyophilized BND nanoparticles.

Characterization of lyophilized BND nanoparticles matrix tablet

Pre compression parameters

Compressibility Studies: The different pre-formulation parameters are studied like angle of repose, compressibility index and hausner's ratio.

Fourier Transform Infrared Spectroscopy (FTIR) Studies: FTIR studies of formulation along with BND and excipients were carried out at room temperature by FTIR. All the spectra were recorded in the range of 400-4000 cm-1.

Post compression parameters

All the prepared lyophilized BND Matrix Tablets were evaluated for the following parameters.

Hardness: Hardness of matrix tablets of lyophilized BND nanoparticles were measured using Monsanto Hardness tester that measures the pressure required to break diametrically placed matrix tablets by applying pressure with coiled spring and the limitations were 1 to 4 kg/cm^2.

Friability: The friability of matrix tablets of lyophilized BND nanoparticles was determined by using Roche friabilator. It was expressed in percentage (%). The friabilator was operated at 25 rpm for 4 min. The tablets were weighted again

$F= [(W-W_0)/W]*100$

Weight Variation: Twenty tablets has been randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.

In vitro drug release study: *In-vitro* dissolution studies of matrix tablets of lyophilized BND nanoparticles were carried out by using USP type II apparatus dissolution apparatus. The matrix tablets were incorporated into 900 ml of simulated gastric fluid (hydrochloric acid solution, pH 1.2) for 2 hr, and then the tablets were transferred to 900 ml of simulated intestinal fluid of phosphate buffer, pH 6.8. This method was used to simulate the situation of a tablet's transit through the gastrointestinal tract. The 10 ml of sample was filtered and obtained filtrate was analyzed by UV analysis method at 357 nm.

RESULT

Optimization of Lyophilized BND

Particle size and zeta potential analysis

Average particle size and zeta potential of lyophilized BND were found to be 453 ± 1.04 nm, and -15.2 ± 0.90 mV respectively

shown in **Figure 1**. Zeta potential plays an important role in the stability of nanosuspension and is a measure of electrostatic stabilization. Despite of having aforementioned value of zeta potential, formulation was found to be quite stable.

Effect of Dissolution on Lyophilized BND

Dissolution study of lyophilized BND was carried out in 0.1N HCl (pH 1.2). Different concentration of polymer is correlated with dissolution of lyophilized BND. The dissolution rate of BND was found 97±0.82% and observed better dissolution compared to pure drug (60±0.25) **Figure 2**. From the experimentation, higher variability was found for the amounts of drug released from the smaller particle size than from the larger ones. This enhanced release could be due to the increase in solubility of drug presented in lyophilized form.

Screening Electron Microscopy

Surface appearance and shape of Lyophilized BND were analyzed by SEM as shown in **Figure 3**. Lyophilized nanoparticles showed uniform size particles of 352 nm. Therefore, it is possible that the reduced particle size, increased surface area and the close contact between the hydrophilic carrier and the drug particles results the enhanced solubility of the BND.

Micromeritic Properties of lyophilized Powder:

The angle of repose of the all the formulations were determined and the values ranged from 20.47 to 26.82 º and that indicate excellent flow properties of powder and it were observed to be within the Pharmacopoeia limits. The Carr's index values ranged from 10.16 to 18.86 % indicates excellent and good flow properties. Hausner's ratio values ranged from 0.80 to 1.26 indicating good flow. It means that the flow properties of lyophilized powder were found to be within the Pharmacopoeia limits. Results are shown in **Table 2**.

Post compression parameters of Matrix Tablet of lyophilized BND nanoparticles

The measured hardness of Matrix tablet of lyophilized BND nanoparticles of each batch was in range from 2.5 to 3.7 kg/cm^2. The % friability of Matrix tablet of lyophilized BND nanoparticles was in the range between 0.34 to 0.75%. The weight variation test was conducted for each batch of all formulations F1 to F9 as per I.P and the results are reflected in **Table 3**. All the Matrix tablet of lyophilized BND nanoparticles passed weight variation test.

***In-vitro* Drug Release Studies**

In formulation F1 minimum amount of HPMC and Chitosan causes extended drug release *i.e.,* about 50 - 60% drug was released

within 10 h, and it was observed 98% of drug releases within 20 h. On exposure to water or biological fluid, generally the dry polymer becomes hydrated, swells and forms a gel barrier layer, which retards the diffusion of drug out of the matrix. In formulation F2 and F3 amount of HPMC increased with decreased amount of lactose, and observed drug release for shorter period of time in comparison to F1 batch. In formulation F4, though drug release extends to considerable period of time till 15 hr, but the tablet of this batch possess less crushing strength cause tablet to disintegrate easily which may be due to higher Chitosan concentration which acts as tablet disintegrate in this batch. When we studied the drug release of Formulation F5, we found tablets of this batch shows extended of drug release due to swelling of HPMC polymer and release pattern may extend till 25 h. Another reason for extended drug release may be due to presence of sufficient amount of lactose in this formulation, which is a water-soluble excipients, it increases the hydration rate and relaxation of the polymer chains, resulting in slow release of drug by diffusion from the matrix tablet layer. So in formulation F5 more than 50% drug release within 10 h, but in Formulation F6, presence of increased HPMC K4 causes less disentanglement or more binding occurs which leads to less % drug release is less in that period of time. In Formulation F7, F8 and F9 drug release in short period of time which may be due to higher concentration of Chitosan cause erosion of tablet. Dissolution profiles of all the batches are shown in **Figure 4**.

Experimental study:

We have formulated different batches to prepare 150 mg of Matrix tablet of lyophilized BND nanoparticles using 3^2 factorial design in order to study the effect of independent variables X_1 and X_2 (i.e. amount of HPMC K4 and Chitosan respectively) on dependent variable (i.e. % drug release in 10 hr (Q_{10}) and time require for 80% drug release (T_{80}) to evaluate extended drug release **Table 4**.

Polynomial equation of 3^2factorial design incorporated for applied design is as follows.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \text{..... (1)}$$

Where Y (Y_1 and Y_2) are the dependent variables, Q_{10} and T_{80}, b_0 is the arithmetic mean response of the 9 runs, b_1 and b_2 are the estimated coefficients for the factors X_1 and X_2, respectively. The fitted equations (full models) relating the responses to the transformed factor which are shown in **Table 5**.

The coefficients b_1, b_2, and b_{22} were found to be significant at $P<0.05$

$Y_1= 58 -10.83 X_1+11 X_2+ 4X_1X_2-1.5 X_1^2- 4 X_2^2$**..... (2)**

$Y_2= 17.55 + 4 X_1- 5.83 X_2 -3.5 X_1X_2 -1.33 X_1^2+2.16 X_2^2$**..... (3)**

It can be concluded from the equation (3) that X_1 showed the more effective than X_2.During the dissolution experiments, it was noticed that HPMC K4 release drug slowly for longer period of time. From the multiple regression analysis, the coefficients b_2 bear a negative sign and R^2=0.989 for time required to release 80% drug from Matrix tablet of lyophilized BND nanoparticles. The coefficients b_1, b_2, and b_{12}, b_{11} were found significant at $P < 0.05$ **(Table 6)**. 3-D response surface plots **Figure 5** and 2-D contour plots **Figure 6** were generated to evaluate response variations against two independent variables using Design Expert.

The polynomial equations can be used to conclude the magnitude of coefficient and the mathematical sign it carries (i.e., positive or negative). A coefficient with positive sign represents a synergistic effect of the factor on the response, while a negative sign will indicate an antagonistic effect. Data analyzed by Microsoft Excel® 2010 version for regression analysis, Analysis of variance (ANOVA). The mathematical relationship in the form of factor's coefficients, its corresponding *P*-values for the measured responses and correlation coefficient are listed in **Table 6** using MLRA.

Concerning %drug release in 10 hr (Q_{10}),the results of multiple linear regression analysis showed from the polynomial equation obtained results of MLRA in case of Y1 showed that the coefficients b_1, b_{11} , b_{22} bear a negative sign and R^2 =0.982. It can be concluded from the equation (2) that X_2 (amount of Chitosan) showed the greater effect compare to X_1(amount of HPMC k4) and negatively impacted. The coefficients b_1, b_2, and b_{12}, b_{22} were found significant at $P < 0.05$ **Table 6**.

FTIR Studies

FTIR spectroscopy was for pure BND and Matrix tablet of lyophilized BND nanoparticles to evaluate compatibility between drug and polymer. Comparative spectra of them are presented in **Figure 7**.

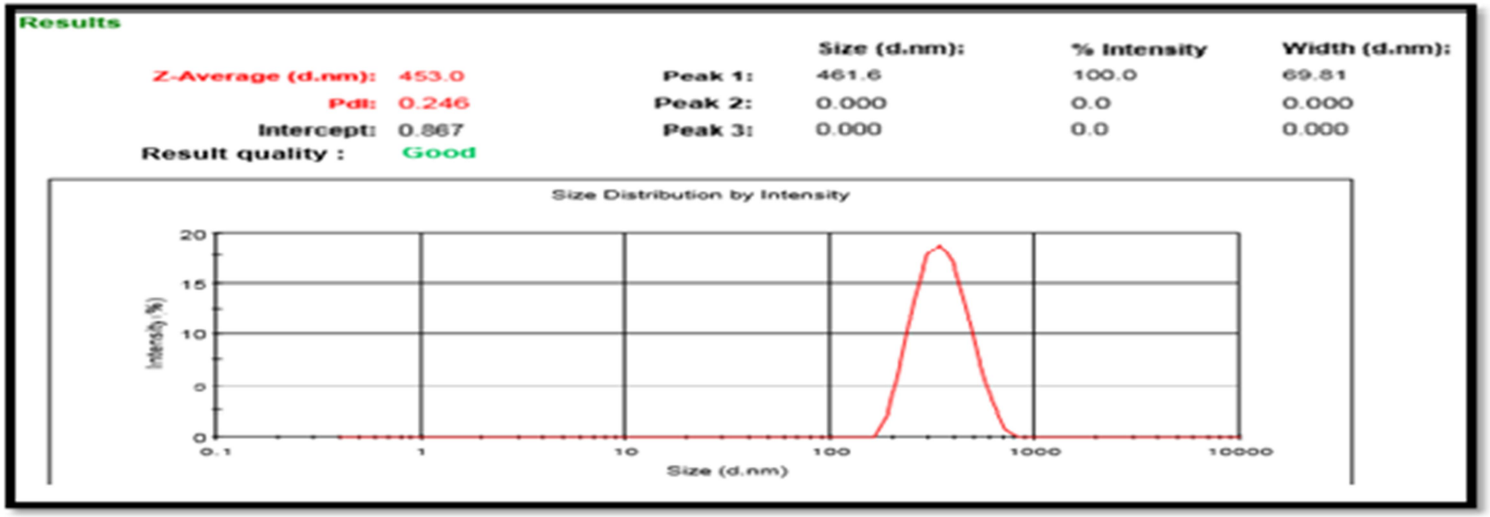

Figure 1 (a): Particle size determination of lyophilized BND

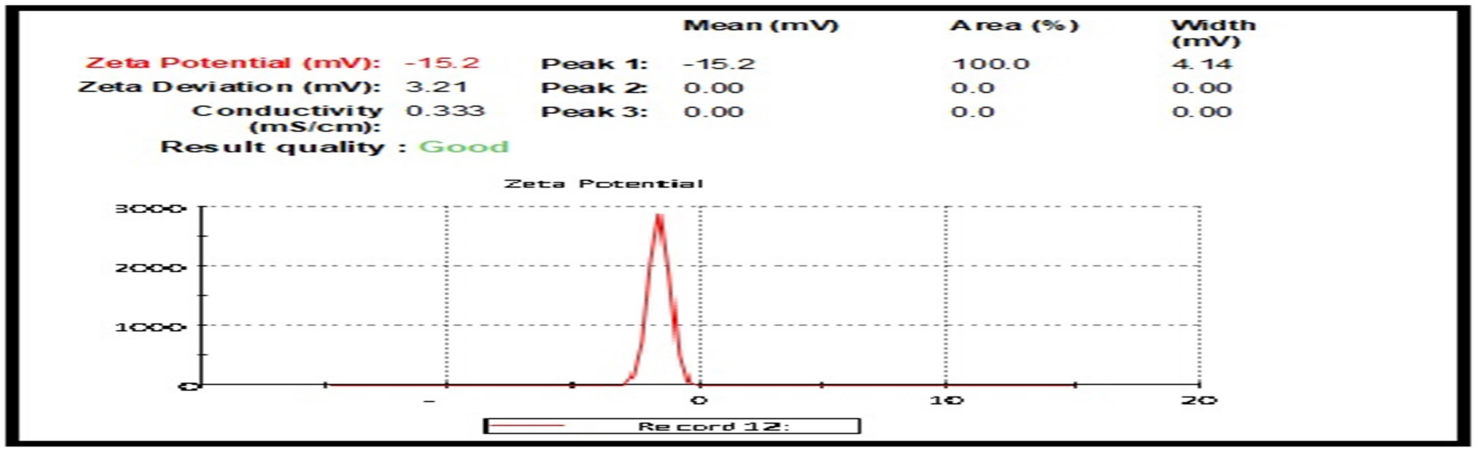

Figure 1 (b): Zeta potential of lyophilized BND

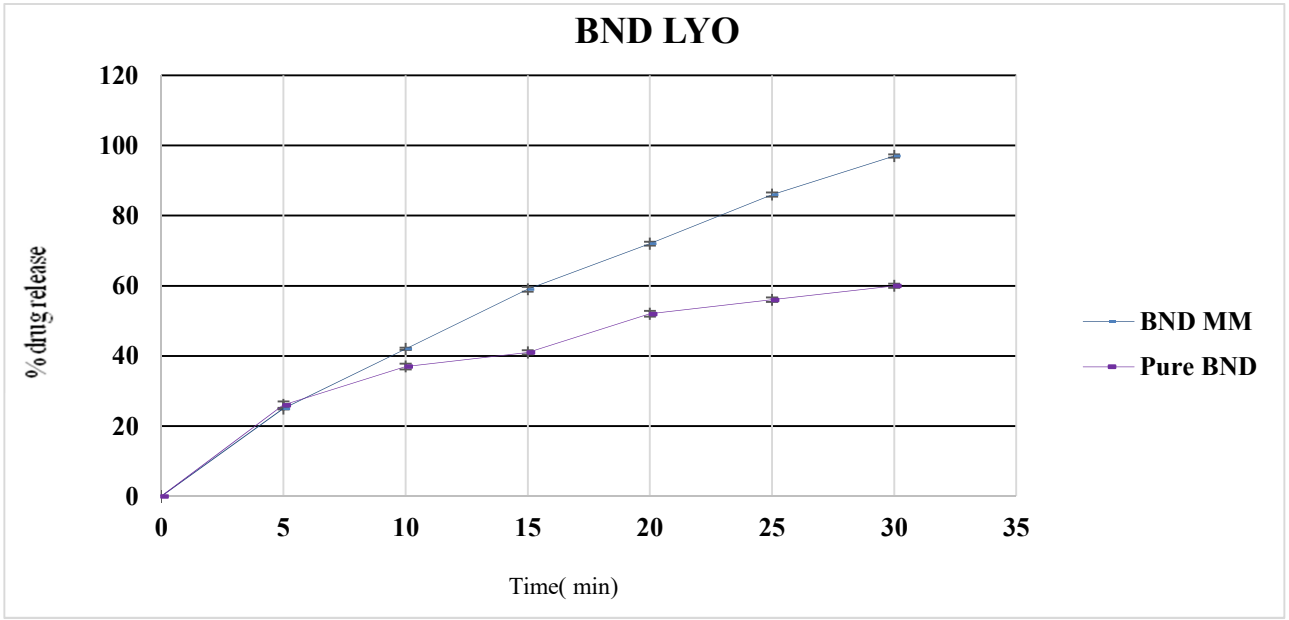

Figure 2: Dissolution studies of lyophilized BND

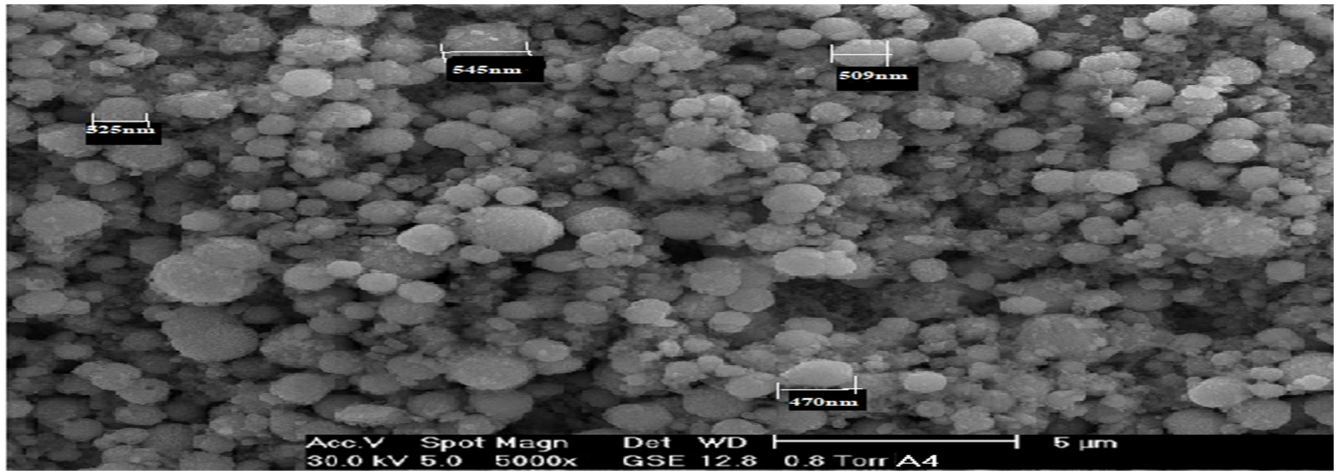

Figure 3: Screening Electron Microscopy of Lyophilized BND

Table 2: Pre Compression Parameters of Lyophilized Powder

Evaluation parameters	F 1	F 2	F 3	F 4	F 5	F6	F7	F8	F9
Angle of Repose	26.82 ± 1.69	22.28 ± 0.91	24.20 ± 0.86	25.46 ± 1.25	24.82 ± 0.90	20.43 ± 1.50	23.91 ± 1.57	21.20 ± 2.05	20.47 ± 1.03
Bulk density	0.47 ± 0.02	0.43 ± 0.01	0.49 ± 0.01	0.46 ± 0.04	0.53 ± 0.02	0.42 ± 0.03	0.46 ± 0.03	0.45 ± 0.07	0.45 ± 0.05
Tapped density	0.57 ± 0.04	0.53 ± 0.02	0.58 ± 0.05	0.55 ± 0.03	0.59 ± 0.01	0.53 ± 0.07	0.57 ± 0.03	0.52± 0.05	0.53 ± 0.03
Carr's Index	17.54 ± 1.02	18.86 ± 0.45	15.51 ± 0.93	16.36 ± 0.37	10.16± 0.60	20.75 ± 1.26	19.29 ± 1.55	13.46 ± 1.60	17.77 ± 1.45
Hausner's ratio	1.21 ± 0.50	1.23 ± 0.27	1.18 ± 0.32	1.19 ± 0.20	1.11 ± 0.12	1.26 ± 0.45	0.80 ± 0.10	0.86 ± 0.08	0.84 ± 0.03

Table 3: Post Compression Parameters of Lyophilized Matrix Tablet

Evaluation parameters	F 1	F 2	F 3	F 4	F 5	F6	F7	F8	F9
Hardness	3 ± 0.01	2.5 ± 0.02	3.5 ± 0.01	3.7 ± 0.02	3 ± 0.01	2.7 ± 0.04	3.1 ± 1.45	2.7 ± 2.04	3.0 ± 1.76
Friability (%)	0.45 ± 0.03	0.39 ± 0.02	0.74 ± 0.01	0.67 ± 0.03	0.34 ± 0.02	0.60 ± 0.01	0.48 ±1.12	0.59 ± 2.15	0.46 ± 2.19
Weight variation	151.73±0.02	149.54±0.06	150.90±0.1	151.74±0.08	149.29±0.07	150.45±0.04	149.81±0.09	150.23±0.03	150.25±0.02

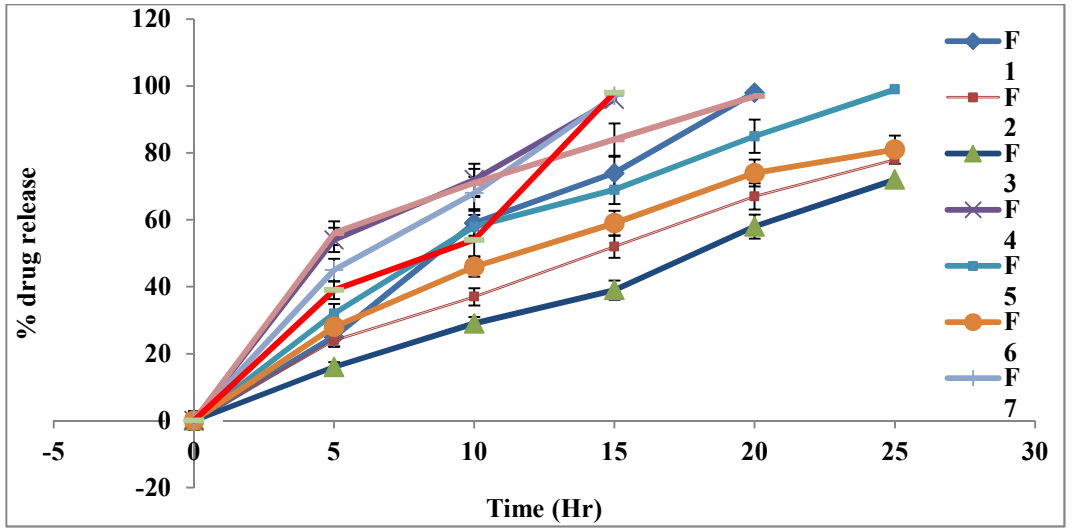

Figure 4: Dissolution studies of lyophilized BND matrix

Table: 4 Variable Level of 3^2 factorial Design for Lyophilized BND Matrix Tablet

Variable Factor	Levels		
	-1	0	+1
Amount of HPMC K4	40	50	60
Amount of Chitosan	15	20	25

Table: 5 Formulation And Dissolution Characteristics of 3^2 Factorial Design Batches

Batch Code	X_1	X_2	Y_1(% drug release in 10 hr(Q_{10}))*	Y_2(time require for 80% drug release (T_{80}) *(hr))
F1	-1	-1	59	17
F2	0	-1	37	27
F3	1	-1	29	30
F4	-1	0	72	11
F5	0	0	58	16
F6	1	0	46	23
F7	-1	+1	68	13
F8	0	+1	71	14
F9	1	+1	54	12

*** Indicates average of three determinations (average±standard deviation, n=3).**

Table 6: Summary of Regression Analysis For Measured Responses

Co- efficients	b_o	b_1	b_2	b_{12}	b_{11}	b_{22}	R^2
Y_1	58	-10.83	11.33	4	1.5	-4	0.982
P-Value	0.0008	0.0184	0.0163	0.025	0.073	0.039	
Y_2	17.55	4	-5.83	-3.5	-1.33	2.16	0.989
P-Value	0.002	0.029	0.010	0.067	0.050	0.098	

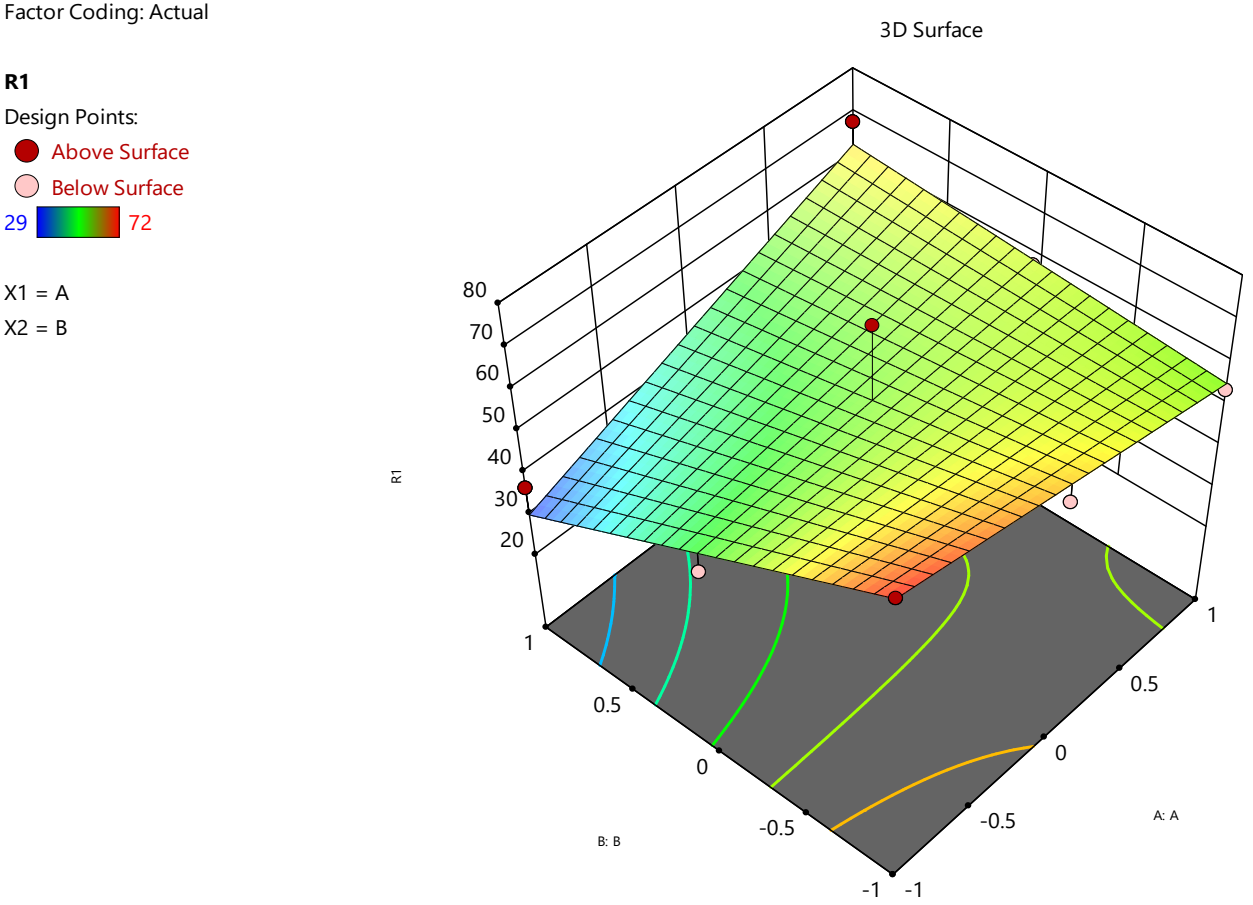

Figure 5 (A): Response surface plot showing Effect of X_1 and X_2 on Y_1 (% drug release in 10 hr)

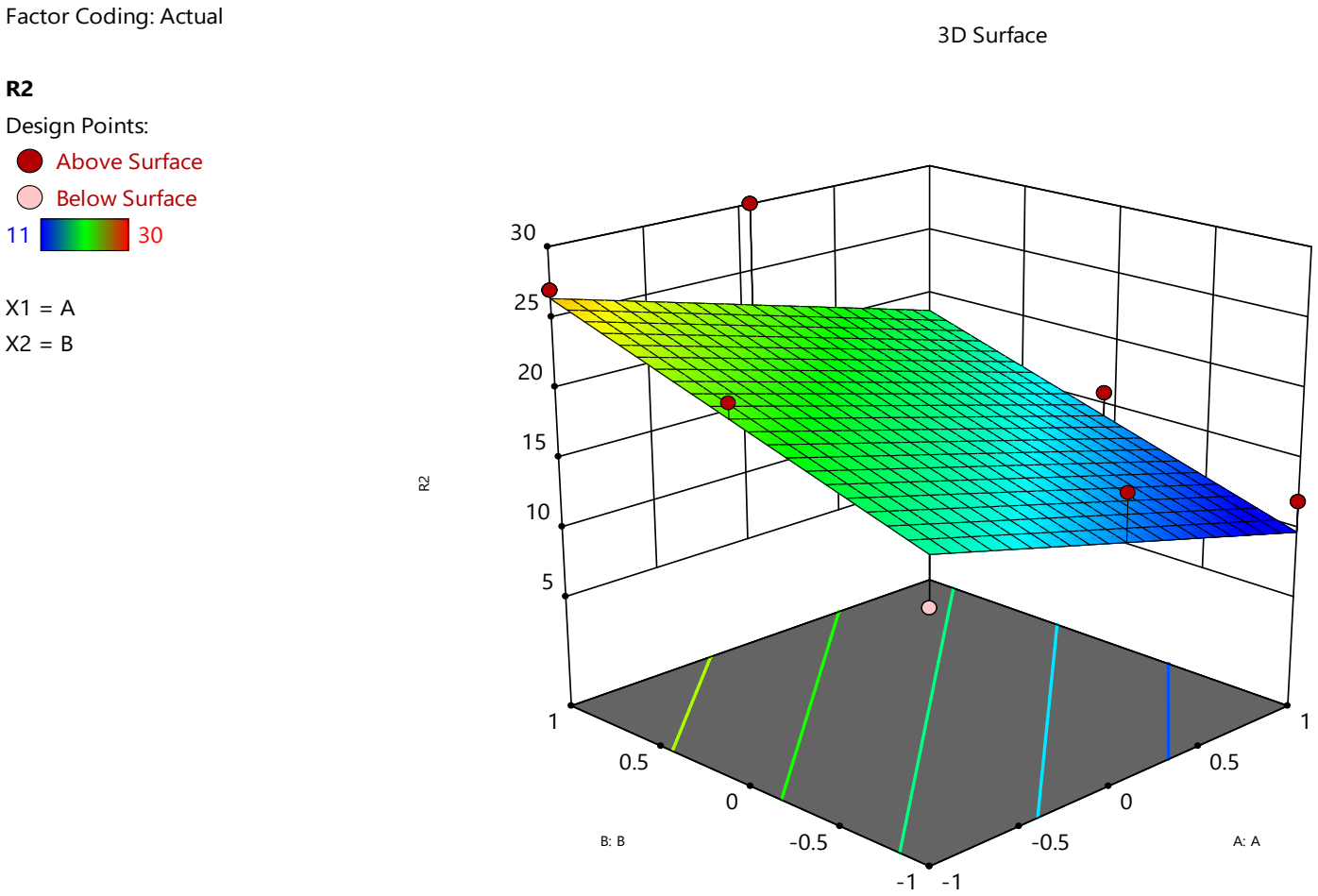

Figure 5 (B): Response surface plot showing Effect of X_1 and X_2 on Y_2 (time require for 80% drug release)

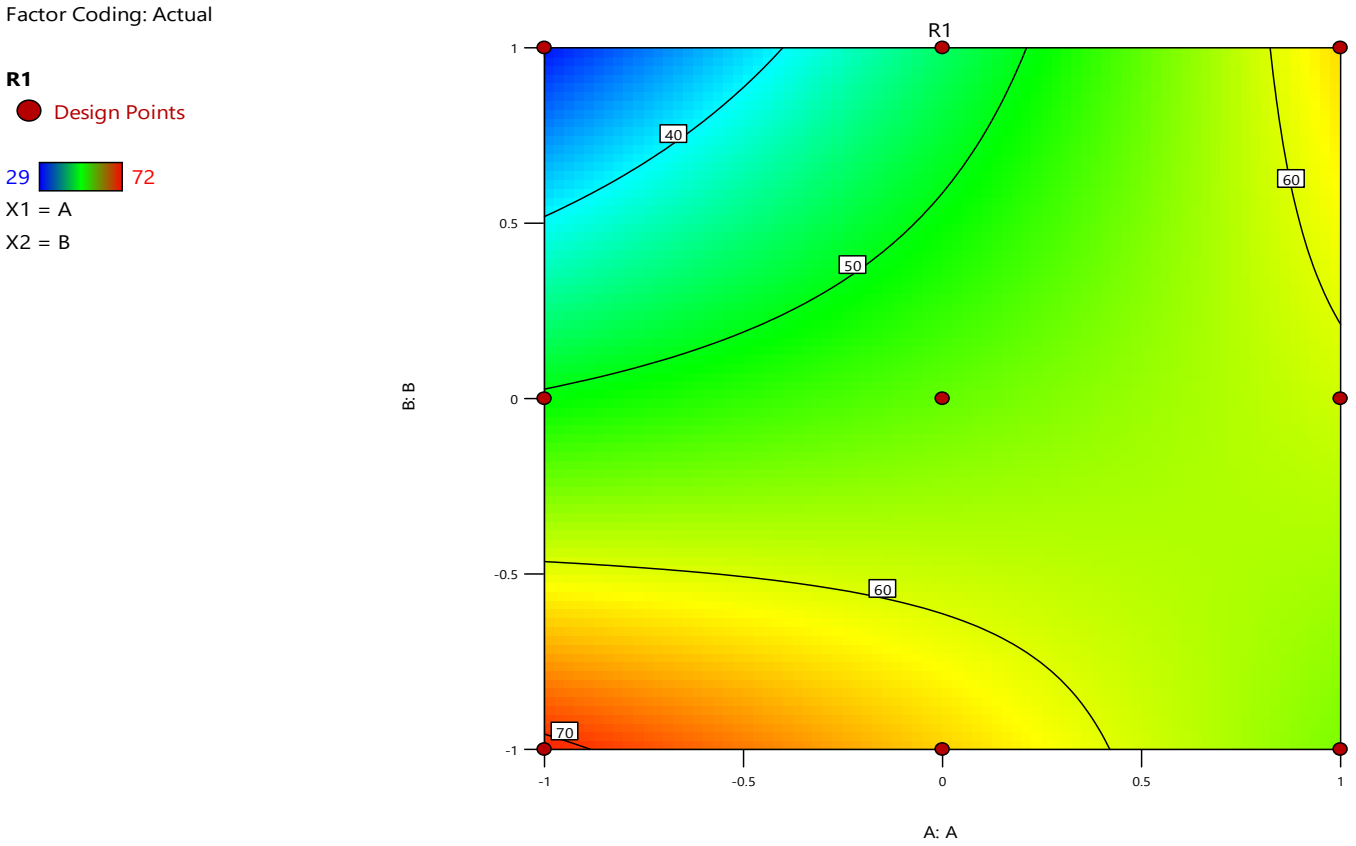

Figure 6 (A): Contour plot showing Effect of X_1 and X_2 on Y_1 (% drug release in 10 hr)

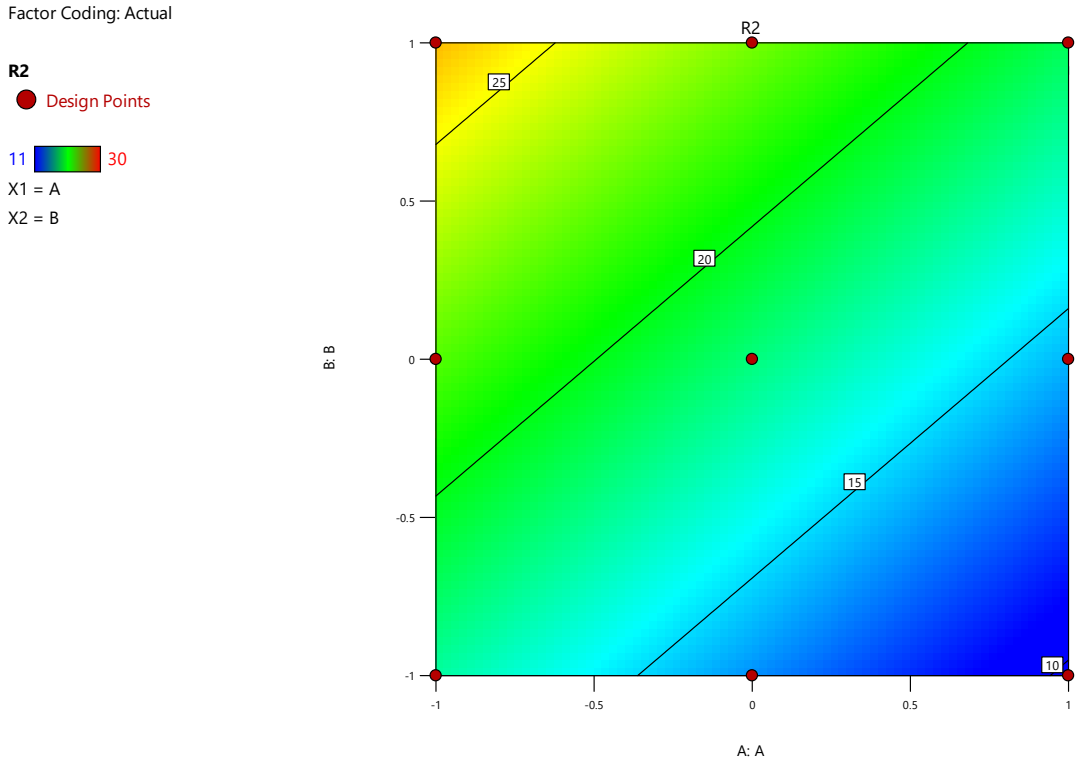

Figure 6 (B): Contour plot showing Effect of X_1 and X_2 on Y_2 (time require for 80% drug release)

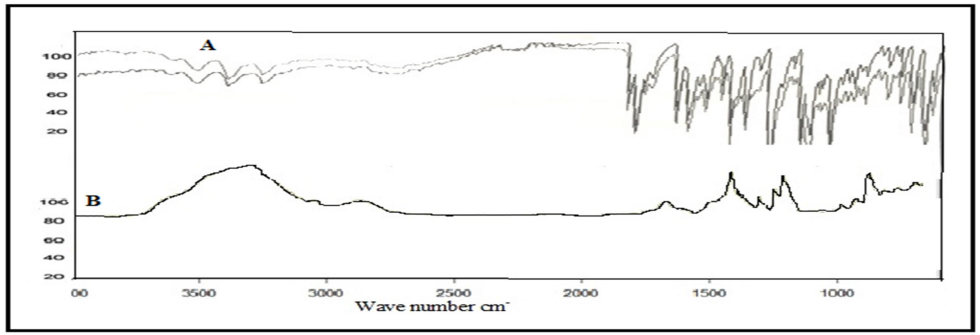

Figure 7: FTIR spectroscopy shows FTIR spectra of Benidipine (A), and lyophilized BND matrix tablet (B)

CONCLUSION

In present research study we have found antihypertensive therapy should be based on achieving consistent blood pressure control over 24 hr, which is possible by formulating a extended release formulation of Benidipine. So, Matrix tablet of lyophilized BND nanoparticles can extend drug release up to 25 hr. The present investigation shows in formulation F5 that HPMC K4 at suitable concentration combined with chitosan can be modified for the extend release in Matrix tablet of lyophilized BND nanoparticles. The physiochemical characterizations of all prepared formulations were found to be satisfactory with various evaluation parameters like angle of repose, bulk density, tapped density, hausner's ratio, hardness, friability, weight variation and drug release study.

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