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Formulation and Evaluation of Nateglinide Sustained Release Tablets

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ABSTRACT

The objective of the present investigation was to design suitable sustained release tablet formulation of Nateglinide by using different polymers such as hydroxy propyl methyl cellulose K15M, xanthan gum, guar gum as release rate retarding polymers. The tablets were prepared by direct compression technique. Nateglinide is used as anti diabetic drug. The objective of the treatment is to achieve hypoglycemia, by using an ideal dosage regimen. The sustained release formulation provides extend duration of action in therapeutic range without reaching toxic levels as in the case of conventional dosage forms. The real formulation trails are carried from F_1 to F_9 in which Drug: Polymer ratio was set as 1:9 respectively. The prepared formulations F_1 to F_9 were evaluated for pre and post compression characteristics, along with the *in vitro* dissolution Studies. It was found that the release of drug from F_1, F_2, and F_3 gave the better release than other formulations. In these three formulations F_2 showing highest release following first order kinetics. From the Higuchi plot good correlation coefficient was observed showing diffusion mechanism. From the peppas plot it was observed that the release model was non fickian anomalous. The release rate was decreased as polymer concentration increased so it shows that increase in diffusion length of polymer decreases the release rate.

Keywords: Nateglinide, sustained release tablets, Hydroxy propyl methyl cellulose K15M, Xanthan gum, Guar gum.

INTRODUCTION

The objective of the present study was to design a sustained release drug delivery system of Nateglinide. It is used as an anti diabetic drug. The objective of the treatment is to achieve hypoglycemia, by using an ideal dosage regimen. Nateglinide is an amino-acid derivative that lowers blood glucose levels by stimulating insulin secretion from the pancreas. This action is dependent upon functioning beta-cells in the pancreatic islets. Nateglinide interacts with the ATP-sensitive potassium (K^+ATP) channel on pancreatic beta-cells. The subsequent depolarization of the beta cell opens the calcium channel, producing calcium influx and insulin secretion. The extent of insulin release is glucose dependent and diminishes at low glucose levels. Nateglinide is highly tissue selective with low affinity for heart and skeletal muscle. The drug is widely used for the management of type-2 diabetes. It has short biological half life (1.5 ± 0.7 h) and bioavailability is 73%. Moreover, site of absorption of Nateglinide is in the intestine. [1-2] The common goal for increased duration is twice a day, or when feasible, once a day. Several properties of the drug itself can lead to the achievement of a 12 to 24 hours oral prolonged release dosage form. Some of the characteristics

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militating against success are very short half life or a relatively large single dose; potent drug with a low margin safety; poorly soluble drug, large first pass metabolism. [3] The short biological half life of the drug favors the development of sustained release formulation. The recommended adult oral dosage of Nateglinide is 60 mg and 120 mg. [4] The specific objective of the research includes developing 9 formulations of Nateglinide using different polymers and evaluation of formulations for pre and post compression parameters along with *in vitro* dissolution studies.

MATERIALS AND METHODS

Nateglinide was obtained as a gift sample from Pharmatrain, Hyderabad. HPMC K15M, xanthum gum, guar gum were received from Dow Chemical Co., USA. Avicel PH 102 was obtained from Colorcon, UK. All other chemicals used were of analytical reagent grade, available commercially and used as such without further processing.

Preparation of Nateglinide sustained released tablet by direct compression technique

All ingredients (model drug + MCC 102 + release retarding polymers) were weighed accurately and co sifted by passing through #40 sieve, blended in a Poly bag for 5 min. The above blend was lubricated with # 60 Sieve passed Magnesium stearate & talc. The formulations were prepared and coded as F_1 to F_9 respectively. The final blend was then compressed into tablets using 16 station tablet compression machine with an average hardness of 4.0 -6.0 kg/cm^2, by using 7 mm die.

Evaluation tests for prepared sustained release tablets: The formulated tablets were evaluated for the following Pre, post compression quality control studies and dissolution studies.

Pre Compression studies [5]

Angle of Repose: It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose of granules was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

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

Where θ = angle of repose; h = height in cms; r = radius in cms

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

Bulk density (BD): It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of granules, which was previously passed through 22 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula.

Bulk density = weight of powder / Bulk volume. $D_b = \frac{M}{V_0}$

M = mass of the powder; V_0 = bulk volume of the powder.

Tapped density (TD): It is the ratio of total mass of powder to the tapped volume of powder

Weigh accurately 25 g of granules, which was previously passed through 22# sieve and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula. Tapped density = Weigh of powder / Tapped volume

$$D_t = (M) / (V_t)$$

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

Carr's Index [6]**:** It is a simple test to evaluate the BD and TD of a powder and the rate at which it was packed down. The formula for Carr's index is as below:

$$\text{Compressibility index} = 100 \times \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

Hausner's Ratio: Hausner's Ratio is a number that is correlated to the flow ability of a powder.

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Post compression studies [7-8]

General appearance: The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.

Weight Variation test: 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not.

Table 1: Formulation of Nateglinide SR tablets by using HPMC K15M, Xanthan gum, Guar gum polymers

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Nateglinide	120	120	120	120	120	120	120	120	120
HPMC K 15M	50	100	150	-	-	-	-	-	-
Xanthum gum	-	-	-	50	100	150	-	-	-
Guar gum	-	-	-	-	-	-	50	100	150
MCC102	145	95	45	145	95	45	145	95	45
Mg. stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
Total	**320 mg**	**320 mg**	**320 mg**	**320 mg**	**320 mg**	**320 mg**	**320 mg**	**320 mg**	**320 mg**

Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

$$\text{Average weight} = \frac{\text{weight of 20 tablets}}{20}$$

$$\%\text{weight variation} = \frac{\text{average weight - weight of each tablet}}{\text{Average weight}} \times 100$$

Thickness: Thickness of the tablets (n=3) was determined using a Vernier Callipers.

Hardness test: Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Friability test: This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting.

Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25 rpm for 4 min. The difference in the weight is noted and expressed as percentage.

It should be preferably between 0.5 to 1.0%.

$$\%\text{Friability} = [(W_1-W_2)/W_1] \times 100$$

Where, W_1= weight of tablets before test, W_2 = weight of tablets after test

Assay of tablets

Weigh and finely powder not less than 20 tablets. Transfer an accurately weighed portion of the powder equivalent to about 10 mg of model drug a 10 ml volumetric flask. Add approximately 6 ml of 6.8 phosphate buffer and shake and sonicate for 10 min to complete the extraction. Dilute the methanol to volume and mix. Pipette 1 ml aliquot into a 10 ml volumetric flask, dilute with mobile phase to volume, mix and filter. From it withdraw take 1 ml aliquot and make up to mark with buffer.

Calculate the quantity in mg of model drug phosphate buffer in the portion taken by the formula

$$\%\text{ drug content} = \frac{\text{actual drug content}}{\text{total drug cotent}} \times 100$$

***In vitro* Dissolution Study** [9]

900 ml of pH-6.8 phosphate buffer was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 37±0.5°C. A tablet was placed in the vessel and was covered; the apparatus was operated up to 12 hours at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} of 211 nm using a UV-spectrophotometer (Lab India).

***In vitro* Release Kinetics Studies** [10]

The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from NDDS was described by using zero order kinetics or first order kinetics. The mechanism of drug release from NDDS was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.

Zero Order Release Kinetics

It defines a linear relationship between the fractions of drug released versus time.

$$Q=k_0t.$$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

$$\text{Log } C= \text{Log } C_o\text{-}Kt/2.303$$

Where C is the amount of drug dissolved at time t, C_o is the amount of drug dissolved at t=0 and K is the first order rate constant.

A graph of log cumulative of log % drug remaining vs time yields a straight line. It will be linear if the release obeys the first order release kinetics.

Higuchi equation: It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

$$Q=K_2t^{1/2}$$

Where K_2 is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

Peppa's - Korsemeyer equation (Power Law): In order to define a model, which would represent a better fit for the formulation, dissolution data was further analysed by Peppa's - Korsemeyer equation (Power Law).

$$Mt/ M_\infty =K.t^n$$

Where, Mt is the amount of drug released at time t, M_∞ is the amount released at time ∞, M_t/M_∞ is the fraction of drug released at time t, K is the kinetic constant and n is the diffusion exponent.

To characterize the mechanism for both solvent penetration and drug release 'n' can be used as abstracted. A plot between log drug release up to 60% against log of time will be linear if the release obeys Peppa's-Korsemeyer equation and the slope of this plot represents "n" value. The kinetic data of the formulations were included.

Nature of release of the drug from the designed tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. The data were processed for regression analysis using MS EXCEL.

Accelerated stability study

There is no much variation in hardness, drug content, and %CDD at the end of 12th hours for the optimized formulation after the accelerated stability studies

Drug-Excipients Compatibility Studies [11]:

Drug Excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions was placed in a vial, rubber stopper was placed on the vial and sealed properly. The compatibility studies is also evaluated by FTIR studies

Procedure: The functional group analysis for the excipients is done using the FTIR (Fourier-transmittance infrared spectroscopy) method of analysis. Initially, the samples (F1, F2, F3, F4, and F5) were made into pellets using a pelletizer under a pressure of 100 kg/cm^2. A blank KBr pellet is made and then a few mg of sample is mixed with KBr and made into pellet. All the pellets are analyzed by PERKIN ELMER FTIR instrument and the data is processed using FTIR system spectrum GX (V5.0.1) version in the wave number range of 4000-400 cm^{-1}

Stability studies: The stability studies of optimized formula were carried out at 40 ± 2°C/75 ± 5% RH using stability chamber for 3 months. The different parameters that were studied are disintegration time, hardness, friability and drug content and dissolution rate. The optimized formulation was found to be stable in terms of physical appearance, drug content, disintegration time and *in vitro* drug release.

Table 2: Acceptance criteria for tablet weight variation (USP 29-NF 34)

Average weight of tablet(mg)	% difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

Table 3: Dissolution Parameters

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	PH-6.8 phosphate buffer
Volume	900 ml
Speed	50 rpm
Temperature	37± 0.5ºC
Sample volume withdrawn	5 ml
Time points	0, 1, 2, 3, 4, 6, 8, 10, 12 hour
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	211 nm

Table 4: Drug Release Kinetics Mechanism

Diffusion exponent(n)	Mechanism
0.45	Fickian diffusion
0.45 < n <0.89	Anomalous(Non- Fickian) diffusion
0.89	Case II transport
n > 0.89	Super Case II transport

RESULTS AND DISCUSSION

Drug-Excipients Compatibility Studies: From the FTIR studies it was clearly concluded that there is no interaction of excipients with the pure drug.

Table 5: Pre compression studies of Nateglinide SR tablets

Formulation Code	Angle of repose (º)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index (%)	Hausner's Ratio
F1	22.17±0.15	0.515±0.015	0.522±0.008	13.15±1.04	1.10±0.07
F2	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.11
F3	25.71±0.13	0.505±0.005	0.527±0.015	14.26±0.65	1.15±0.31
F4	23.31±0.13	0.522±0.023	0.519±0.022	12.36±0.26	1.09±0.23
F5	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.11
F6	25.71±0.13	0.505±0.005	0.527±0.015	14.26±0.65	1.15±0.31
F7	23.31±0.13	0.522±0.023	0.519±0.022	12.36±0.26	1.09±0.23
F8	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.11
F9	31.11±0.11	0.471±0.011	0.476±0.012	16.23±0.23	1.21±0.11

Table 6: Post compression studies of Nateglinide SR tablets

Formulation Code	Avg. Wt (mg) (n=20)	Thickness (mm) (n=3)	Hardness (kp) (n=3)	*% Friability	% Drug content (n=3)
F1	320.5±0.5	4.82±0.34	5.4±0.418	0.59	99.98±0.18
F2	319.9±0.1	4.91±0.23	4.7±0.273	0.68	93.02±0.10
F3	320.9±0.9	4.84±0.1	5.7±0.346	0.58	99.67±0.12
F4	319.7±0.3	4.88±0.1	5.2±0.188	0.59	100.32±0.14
F5	320.6±0.6	4.84±0.1	5.4±0.394	0.58	99.67±0.12
F6	319.4±0.6	4.91±0.23	5.8±0.263	0.68	100.21±0.20
F7	316.4±0.6	4.82±0.34	5.3±0.329	0.59	99.98±0.18
F8	319.2±0.8	4.91±0.23	5.6±0.152	0.68	100.21±0.20
F9	319.6±0.4	4.84±0.1	5.6±0.245	0.58	99.67±0.12

Table 7: *In-vitro* Dissolution results of Formulations F_1 to F_9

S. No.	Time (h)	% Cumulative Drug released								
		F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	0	0	0	0	0	0	0	0	0	0
2	1	25	18	12	40	38	37	40	38	37
3	2	42.23	22	18	62	59	56	62	59	56
4	3	51	43	39	85	81	80	85	81	80
5	4	68	51	43	100	95	91	100	95	91
6	6	75	69	54.18	100	100	98	100	100	98
7	8	86	76	68	100	100	100	100	100	100
8	10	93	84	75	100	100	100	100	100	100
9	12	97	93	84	100	100	100	100	100	100

Table 8: Characterization of Release Kinetics

Formulation Code	R^2 Square Value				n Value
	Zero order	First order	Higuchi plot	Korsemeyer-peppas plot	
F1	0.678	0.984	0.983	0.201	0.580
F2	0.871	0.978	0.960	0.085	0.420
F3	0.914	0.990	0.945	0.252	0.580
F4	0.020	0.987	0.767	0.520	0.501
F5	0.092	0.937	0.814	0.470	0.598
F6	0.167	0.982	0.843	0.450	0.540
F7	0.720	0.973	0.504	0.790	0.560
F8	0.430	0.991	0.646	0.720	0.560
F9	0.360	0.989	0.679	0.701	0.530

Table 9: Accelerated stability data for Optimized formulation (F2)

Stability Studies for best formulation (F_2)	Initial	At 40 ± 2°C/ 75 ± 5% RH (After 1 Month)	At 40 ± 2°C/ 75 ± 5% RH (After 2 Month)	At 40 ± 2°C/ 75 ± 5% RH (After 3 Month)
Physical appearance /Color	White	White	White	White
Weight Variation (g)	0.319±1%	0.3188±1.2%	0.318±2%	0.317±3%
Hardness (kg/cm²)	5.4±0.16	5.38±0.16	5.35±0.16	5.3±0.21
Friability (%w/w)	0.61%	0.60%	0.59%	0.58%
%CDD at 12 hours	99.23±0.2%	98.22±0.2%	97.21±0.2%	96.21±0.25%

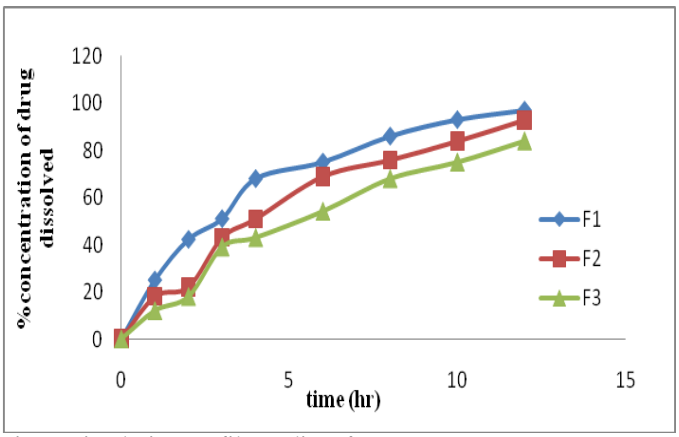

Fig. 1: Dissolution profile studies of F1, F2, F3

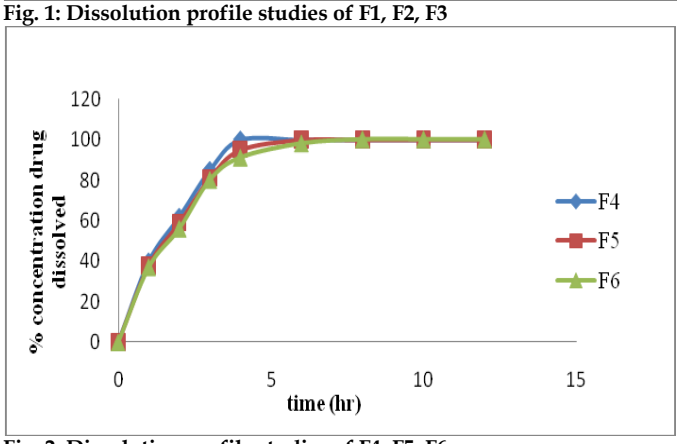

Fig. 2: Dissolution profile studies of F4, F5, F6

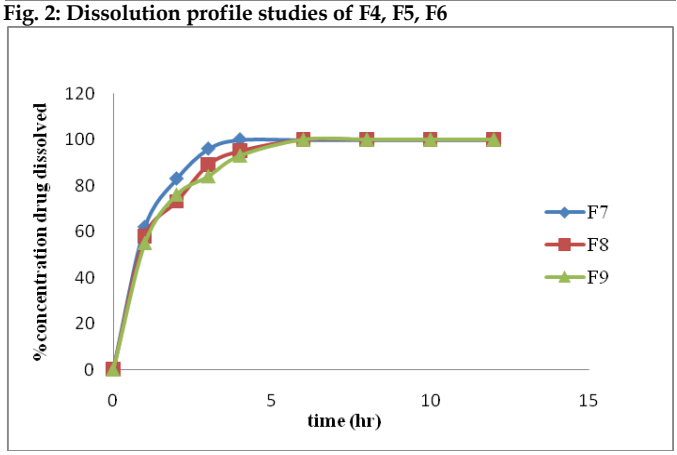

Fig. 3: Dissolution profile studies of F7, F8, F9

Formulation of SR Tablets by direct compression: The formulations were prepared with, HPMC K15M, xanthan gum, guar gum as release rate retarding polymers by direct compression method. The formulations were evaluated for pre & post compression characteristics, along with *in vitro* dissolution Studies.

Pre Compression studies on the directly compressible blends of SR Nateglinide: The angle of repose values obtained for all the formulations are between 21° to 30°. This indicates excellent flow property of the powder blends. The compressibility index values for all the formulations are in between 10 to 19. This indicates the powder blends have good flow property.

Post compression studies on SR of Nateglinide tablets: The tablets thickness was also used to assess the quality of the tablet under uniform conditions of manufacturing process. Thickness of the tablets ranged from 4.83- 5.1 mm. The total weight of each formulation was not maintained uniformly however the weight variation of the tablets within the limits of ± 1%. The measured hardness of tablets in all batches was ranged from 4-6 kg/cm². Friability values were found to be less than 1% in all prepared formulations and considered to be satisfactory.

***In vitro* Dissolution Study**

The real formulation trails are carried form F_1 to F_9 in which Drug: Polymer ratio was set as 1:9 respectively. Further the formulation F_2 is selected as better/ optimized formulation, taken a big batch to charge in stability studies. From the above results it was found that the release of drug from F_1, F_2, F_3 gave the better release than other formulations. In these four formulations F_2 showing highest release when we compare the r^2 value for zero order and first order graphs for F_2 it shows that was following first order kinetics because r^2 of first order is more than r^2 value of zero order.

From the graph and r^2 values (Table 8). It was observed that the Higuchi plot r^2 values for F_2 is 0.962 which is

showing good correlation coefficient so it was following diffusion mechanism. From the peppas plot it was observed that diffusion coefficient values was in the range of 0.45 to 0.89 (0.534) which indicated the release model was non fickian anomalous. The release rate was decreased as polymer concentration increased so it shows that increase in diffusion length of polymer decreases the release rate.

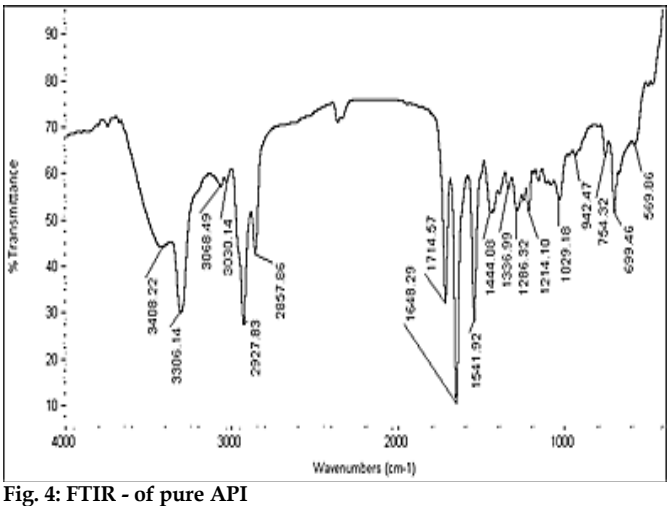

Fig. 4: FTIR - of pure API

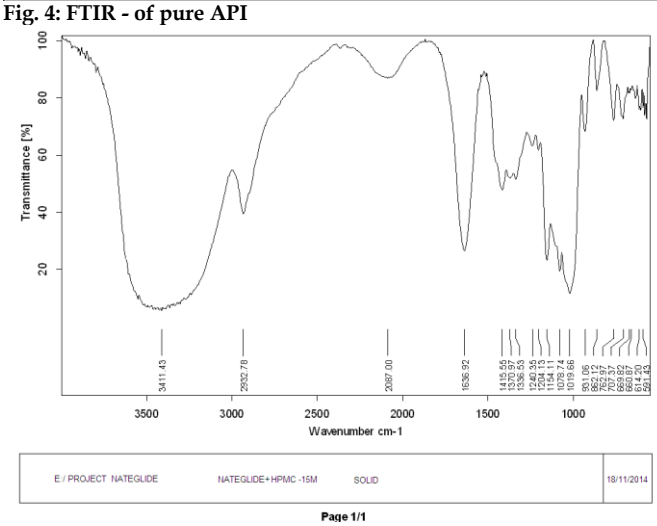

Fig. 5: FTIR of Drug + HPMC K 15M

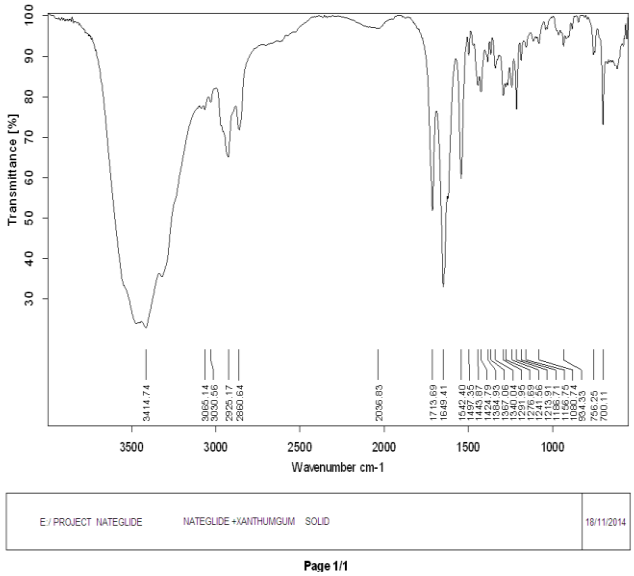

Fig. 6: FTIR of Drug +Xanthan gum

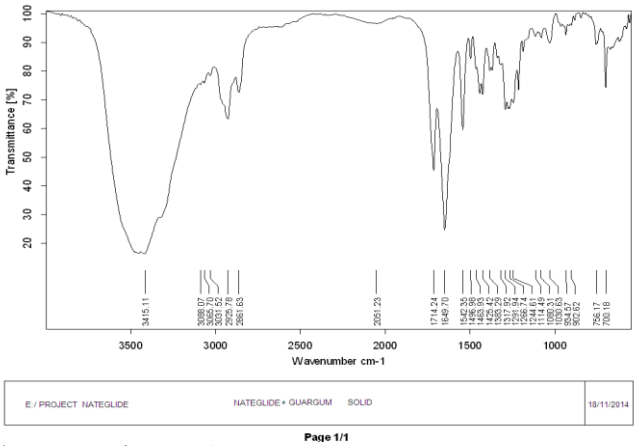

Fig. 7: FTIR of Drug +Guar gum

Accelerated stability studies of optimized formulation: There is no much variation in hardness, drug content, friability and %CDD at the end of 12th hours for the optimized formulation after the accelerated stability studies. The physicochemical incompatibilities of the drug/API with excipients in the optimized formulation (F_2) were tested by analyzing FTIR studies concluded that there is no interaction with excipients.

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