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Formulation and evaluation of oral disintegrating tablets of nateglinide

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ABSTRACT

The present study aims to formulate and evaluate oral disintergrating tablet of nateglinide, a drug that is used for the treatment of non-insulin dependent diabetes milletus was prepared by using different polymers and also optimize the best formulation. The study involved different excipents which were tested for their compatibility with nateglinide by the FT-IR studies. Based on the results of FT-IR studies, majority of the excipients were found to be compatible with nateglinide which were used for the preparation of nateglinide oral disintegrating tablets. nateglinide is an oral anti-diabetic agent agent used for the treatment of non-insulin dependent diabetes milletus. Oral disintegrating tablets of of nateglinide were prepared by direct compression method by the addition of superdisintegrants. Nine batches (F1-F9) of oral disintegrating tablets of nateglinide were prepared by using superdisintegrants like Crosspovidone, Croscromellose Sodium and Sodium starch glycolate in variable concentrations along with other excipents for the development of optimized formulation. All the formulations were subjected to evaluation studies of weight variation, hardness, friability, drug content, in-vitro disintegration, in-vitro-dissolution studies and are found to be within the limits.

Key words: Oral disintegrating tablet (ODT), Nateglinide, Direct compression, Anti-Diabetic activity.

INTRODUCTION

Most of the drugs are frequently taken by oral route. Vast numbers of drugs are swallowed in the mouth but some of them are intended to be dissolved before taken in the mouth. The oral route has been the most popular and successfully used for the delivery of the drug when compared with alternate routes of drug delivery. It is considered as the most natural, safe and helps in offering flexibility in the design of the dosage form and low cost. [1] Tablets constitute a major portion of the drug delivery systems that are currently available. However, many patient groups such as elderly, children, and patients mentally retarded, uncooperative, nauseated, or on reduced liquid intake diets have difficulty in swallowing these dosage forms. Many elderly persons face difficulties in swallowing because of hand tremors and dysphasia. In some cases like motion sickness, sudden episodes of allergic attack, it results in high occurrence of noncompliance and ineffective therapy.[2] To fulfill these medical needs and improve the quality of treatment considerable efforts are made to develop a novel type of dosage form for oral administration known as oral disintegrating tablets to get dissolved in the mouth with help of water soluble polymers.[3] ODT tablets were prepared by using superdisintegrants such as crosspovidone, crosacromellose sodium and sodium starch glycolate which provide rapid disintegration of the tablet in mouth. Many techniques are provided to achieve ODT like direct compression, tablet moulding, spray drying, cotton candy process, mass extrusion and freeze drying.[4] Of all these above mentioned techniques, direct compression technique is most conveniently used as it does not require any special manufacturing process.[3] The present study aims to formulate oral disintegrating tablets of nateglinide with

the help of superdisintegrants and to characterize any drug-polymer interactions and to evaluate the release kinetics by in-vitro dissolution studies.

MATERIALS AND METHODS

Nateglinide was obtained as a gift sample from Cipla Ltd; Mumbai. Crosacromellose sodium, Crospovidone, Sodium starch glycolate, magnesium stearate and lactose were purchased from S.D. Fine chemicals, Mumbai.

Calibration curve of nateglinide

Calibration curve of nateglinide was prepared by using phosphate buffer pH 6.8. The drug was analyzed spectrophotometrically **(**Elico Double beam UV-Visible Spectrophotometer**)** at 209 nm.
(regression coefficient R^2 = 0.999 in buffer Ph 6.8) and graph is shown in fig 1.

Drug-excipient interaction studies

Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with polymers. Positive interactions sometimes have a beneficial effect as far as desired release parameters are concerned. Therefore, in the present studies nateglinide with the given polymers were analyzed for compatibility studies. The spectra are shown in figure 2 - 5.

Pre-compression studies [5]

All the physical parameters namely, angle of repose, bulk density, compressibility index and Hausner's ratio were performed and the results are shown in table 2

1. Angle of Repose:

It is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Angle of Repose 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 given formula.

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

2. Bulk density :

It is the ratio of total mass of powder to the bulk volume of powder. Required quantity of powder blend was transferred in 100 ml graduated cylinder and the bulk density was calculated by using the formula given below.

Bulk density = weight of powder/ Bulk volume.

3. Tapped density:

It is the ratio of total mass of powder to the tapped volume of powder.Required quantity of powder blend was transferred in 100 ml graduated cylinder which was operated for fixed number of taps until the powder bed volume has reached a minimum Tapped density using the was calculated by formula given below.

Tapped density = Weigh of powder / Tapped volume

4. Compressibility Index:

It is a simple test to evaluate bulk and tapped density of a powder .The formula for Carr's index is as below:

$$\text{Compressibility index} = 100 \times \frac{\text{Tapped Density} - \text{Bluk Density}}{\text{Tapped Density}}$$

5. Hausner's Ratio:

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

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

TABLET PREPARATION METHOD

Oral Disintegrating Tablets of nateglinide were prepared by using direct compression technique according to the composition of tables shown in the table 1. This method involves a simple procedure of blending of API with other ingredients and the resulted mixture is subjected to direct compaction. [6] The required ingredients were taken in a mortar and the powder blend was mixed for a time period of 15-20 min by using mortar and pestle. Then each mixture was passed through sieve no.60 and finally magnesium stearate was added as lubricant and thoroughly mixed. It was then compressed by using 16 station tablet compression machine (Cadmach India Ltd.) to produce flat faced tablets each weighing 235mg.

POST COMPRESSION STUDIES

1. Weight Variation

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. 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.

2. Hardness test

Hardness of the tablet was determined by using the Monsanto hardness tester-Mumbai. 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.

3. 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 Roche friabilator, rotating at 100rpm for 4min. The tablets are then taken out, dedusted and were weighed.The difference in the weight is noted and expressed as percentage.

4. Wetting Time

Circular tissue papers were placed in a petridish containing water. The prepared tablet was then carefully placed. The time required for water to reach the upper surface of the tablets and to get completely wet was noted as the wetting time. Wetting time was recorded using a stopwatch.

5. In- Vitro Disintegration Time

In- vitro disintegration time was measured by dropping a tablet in a beaker containing phosphate buffer P^H 6.8. Tablets from each formulation were randomly selected and in vitro dispersion time was performed. All these studies were performed and the results are shown in tables 3- 4.

In-vitro drug release studies:

In-vitro drug release studies were carried out by using USP-type II dissolution apparatus.

900 ml of Phosphate buffer (pH 6.8) was placed in the dissolution flask maintained at a temperature of 37 ± 0.5^0C.One tablet was placed in the flask of the dissolution apparatus and was operated to run upto 60mins at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn, filtered and again replaced with 5 ml of fresh medium. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} is 209 nm using a UV-spectrophotometer (Lab India; Mumbai). The in-vitro drug release of ODT tablets of nateglinide were shown in fig 6 -8 and their comparision profile was shown in fig 9.

DATA ANALYSIS

Different release kinetics is assumed to reflect different release kinetics mechanism. Therefore three kinetics models including zero order release equation (Eq.1), first order equation (Eq. 2) and Higuchi (Eq .3) were applied to process in vitro data to find the equation with the best fit.

Q = K1t (Eq .1)

Q = 100 (1-e-K2t) (Eq. 2)

Q = KHt1/2 (Eq. 3)

Where Q is the release percentage at time t. K1, K2 and KH are the rate constant of zero order, first order and Higuchi model respectively. To investigate the mechanism of drug release the in vitro data were plotted as cumulative drug release verses square root of time as described by higuchi, when the linearity was observed in graph that indicates the diffusion controlled release mechanism of drug.[7] The dissolution data was further analysed to define the mechanism of release by applying the dissolution data following empirical equation proposed by peppas, Mt/Mα=Ktn where Mt is drug release at time t, Mα is the total amount of drug in dosage form, Mt/Mα is the fraction of drug release up to time t, K is the kinetic constant and "n" is the release exponent indicative of the release mechanism of drug release from the formulation during dissolution process.[8]

RESULTS AND DISCUSSION

Fig 1. Calibration curve of Nateglinide

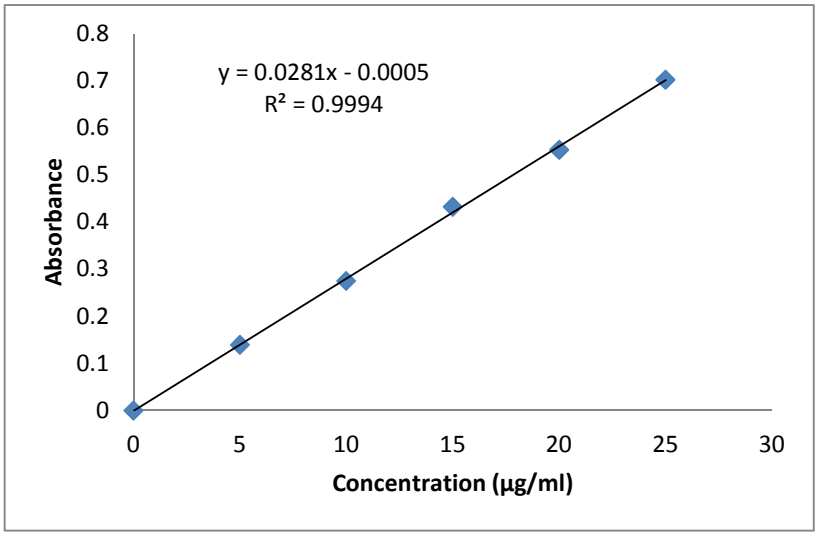


Table 1. Composition of oral disintegrating tablets of Nateglinide

		FORMULATIONS								
S. No	INGREDIENTS(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	NATEGLINIDE	60	60	60	60	60	60	60	60	60
2	CROSACRAMELLOSE SODIUM	5	10	15				-	-	-
3	SODIUM STARCH GLYCOLATE	-	-	-	5	10	15	-	-	-
4	CROSPOVIDONE	-	-	-	-			5	10	15
5	MANNITOL	110	110	110	110	110	110	110	110	110
6	ASPARTAME	5	5	5	5	5	5	5	5	5
7	LACTOSE	50	50	50	50	50	50	50	50	50
8	MG. STEARATE	3	3	3	3	3	3	3	3	3
9	TALC	2	2	2	2	2	2	2	2	2

FT-IR STUDIES

To study the presence of interactions between the active pharmaceutical ingredient and the selected polymers, FT-IR studies were undertaken. The The FT-IR spectra are shown in Figure 2 to 5

Fig 2. FT-IR Spectra of Nateglinide

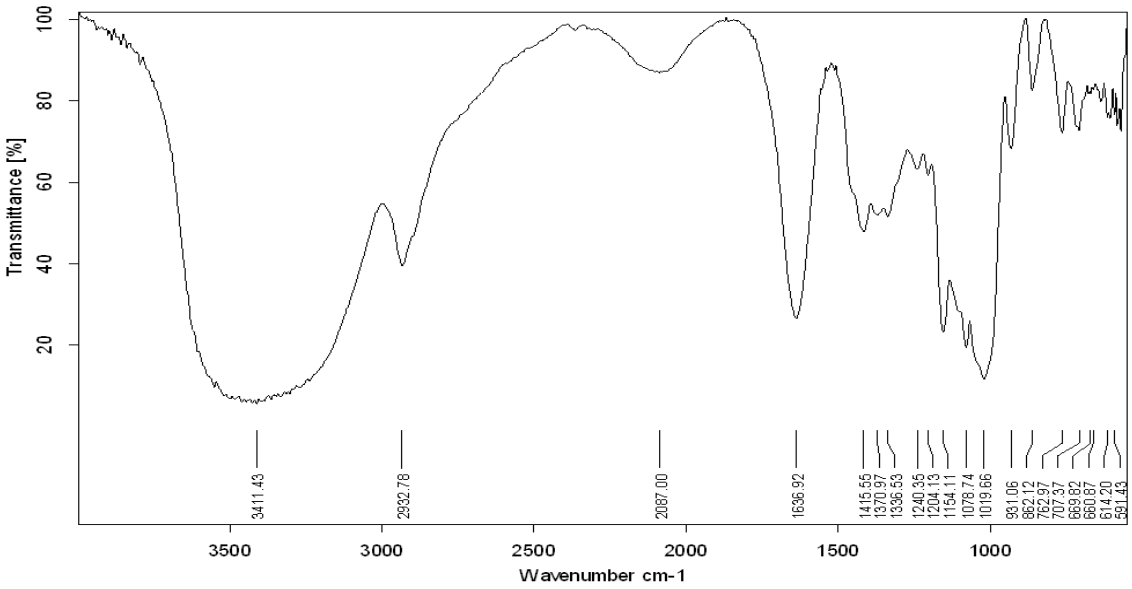


Fig 3. FT-IR Spectra of Nateglinide and Crospovidone

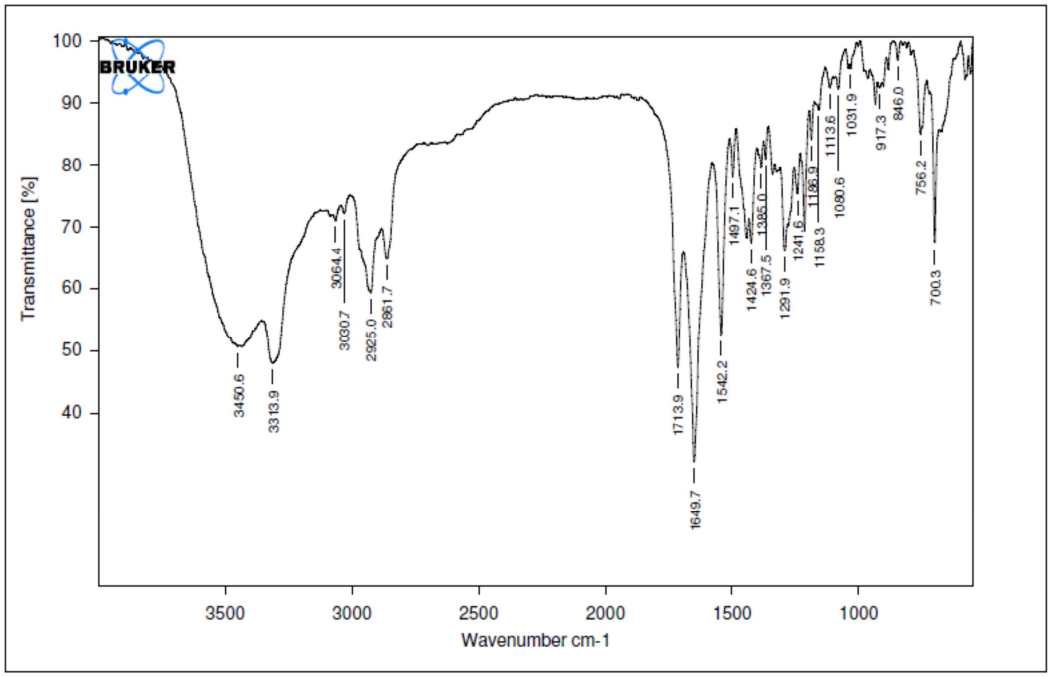


Fig 4. FT-IR Spectra of Nateglinide and Crosacramellose sodium

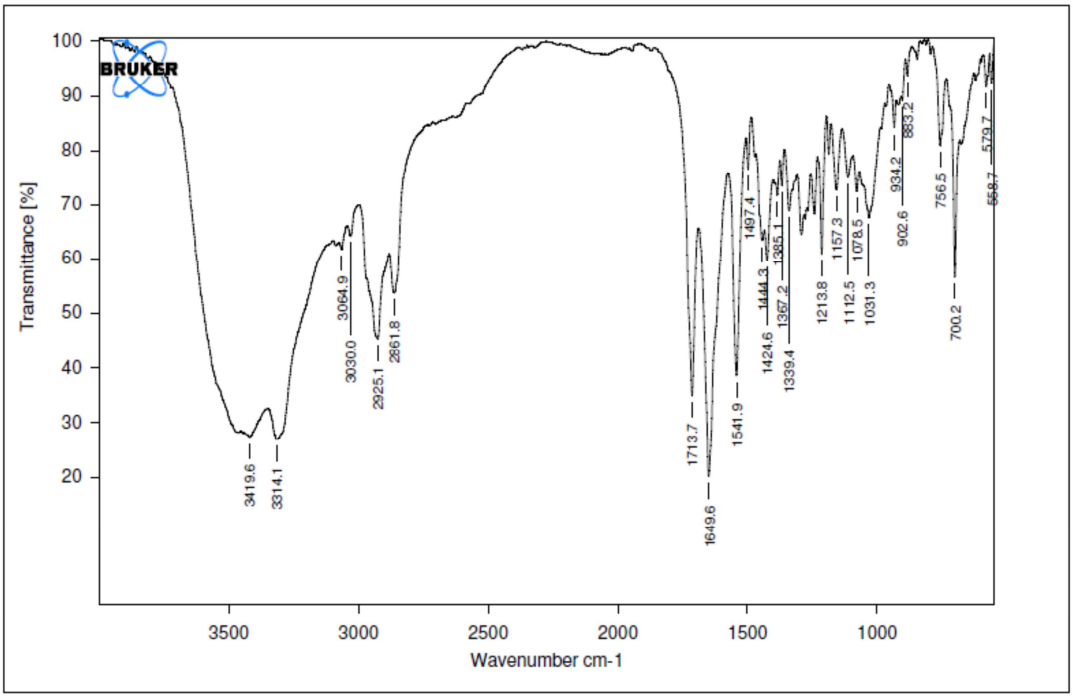


Fig 5. FT-IR Spectra of Nateglinide and Sodium starch glycolate

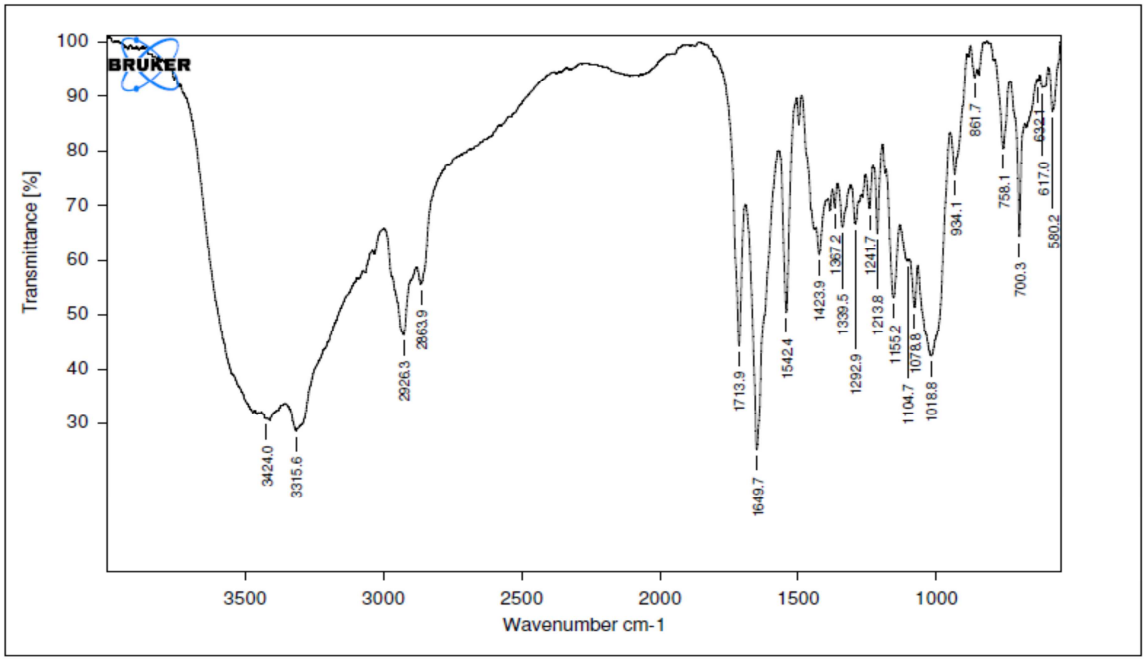


Table 2. Pre Compression parameters of Nateglinide tablet formulation

S. No	Formulation	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of repose (θ)	compressibility index	Hausner's ratio
1	F1	0.96±0.12	0.98±0.10	27.3±0.15	12.6	1.11
2	F2	0.86±0.12	0.96±0.12	31.2±0.13	12.1	1.14
3	F3	0.85±0.13	0.98±0.10	35.6±0.12	13.6	1.16
4	F4	0.94±0.10	0.95±0.13	29.6±0.13	15.1	1.18
5	F5	0.89±0.15	0.93±0.14	25.3±0.12	14.3	1.17
6	F6	0.82±0.11	0.95±0.12	29.2±0.09	06.6	1.07
7	F7	0.85±0.12	0.94±0.10	31.6±0.12	11.9	1.13
8	F8	0.91±0.10	0.89±0.09	29±0.10	10.9	1.12
9	F9	0.89±0.13	0.93±0.10	34±0.12	14.3	1.17

** n=3 , Mean ±SD*

Table 3. Post Compression Parameters of ODT of Nateglinide

S.No.	Formulation	Weight variation	Hardness (kg/cm^2)	Friability (%)	% Drug content
1	F1	208.89±0.12	3.2±0.13	0.73±0.15	95.12
2	F2	209.12±0.13	3.1±0.12	0.71±0.13	96.10
3	F3	209.64±0.14	2.9±0.13	0.67±0.14	95.14
4	F4	208.92±0.12	3.0±0.10	0.63±0.12	97.10
5	F5	209.67±0.13	3.2±0.12	0.65±0.10	96.12
6	F6	208.82±0.10	3.1±0.10	0.66±0.12	97.08
7	F7	210.05±0.09	3.0±0.12	0.63±0.10	96.12
8	F8	208.03±0.10	3.1±0.09	0.61±0.12	98.10
9	F9	210.12±0.12	3.2±0.10	0.62±0.10	97.12

** n=3 Mean ±SD*

Table 4. Post Compression Parameters of ODT of Nateglinide

S.No.	Formulation code	Thickness (mm)	In-vitro Disintegration Time (sec)	Wetting Time (sec)
1	F1	2.5±0.12	34±0.10	45±0.14
2	F2	2.7±0.10	28±0.13	42±0.13
3	F3	2.8±0.13	25±0.10	39±0.14
4	F4	2.7±0.10	26±0.09	37±0.12
5	F5	2.6±0.12	27±0.10	39±0.13
6	F6	2.5±0.10	25±0.12	37±0.10
7	F7	2.7±0.11	26±0.10	34±0.09
8	F8	2.6±0.12	21±0.13	31±0.10
9	F9	2.5±0.10	24±0.12	33±0.12

** n=3 Mean ±SD*

Fig 6. In-vitro drug release profiles of ODT of Nateglinide (F1-F3)

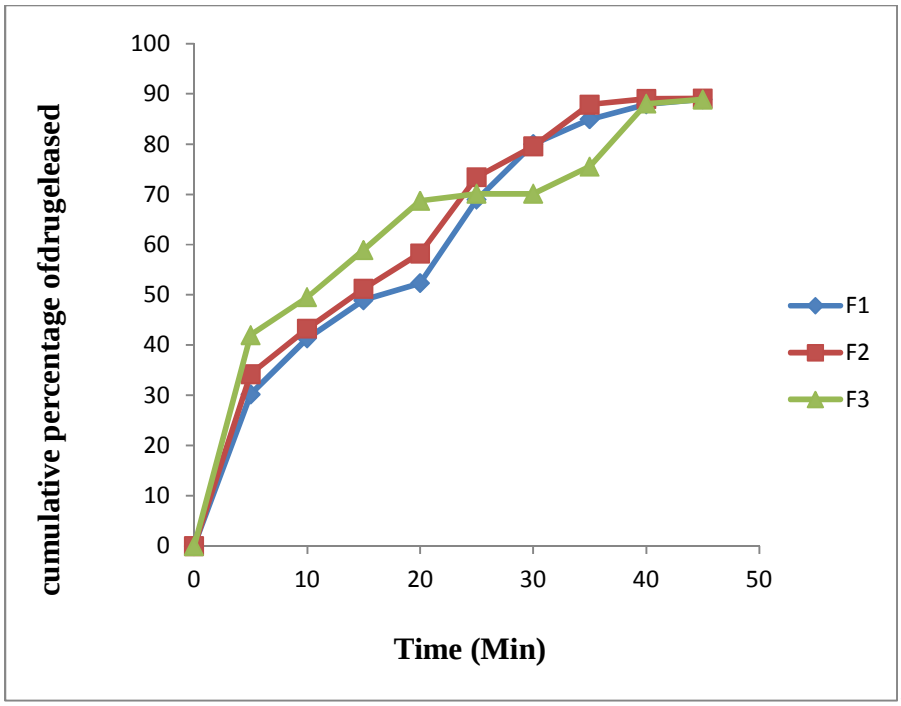


Fig 7. In-vitro drug release profiles of ODT of Nateglinide (F4-F6)

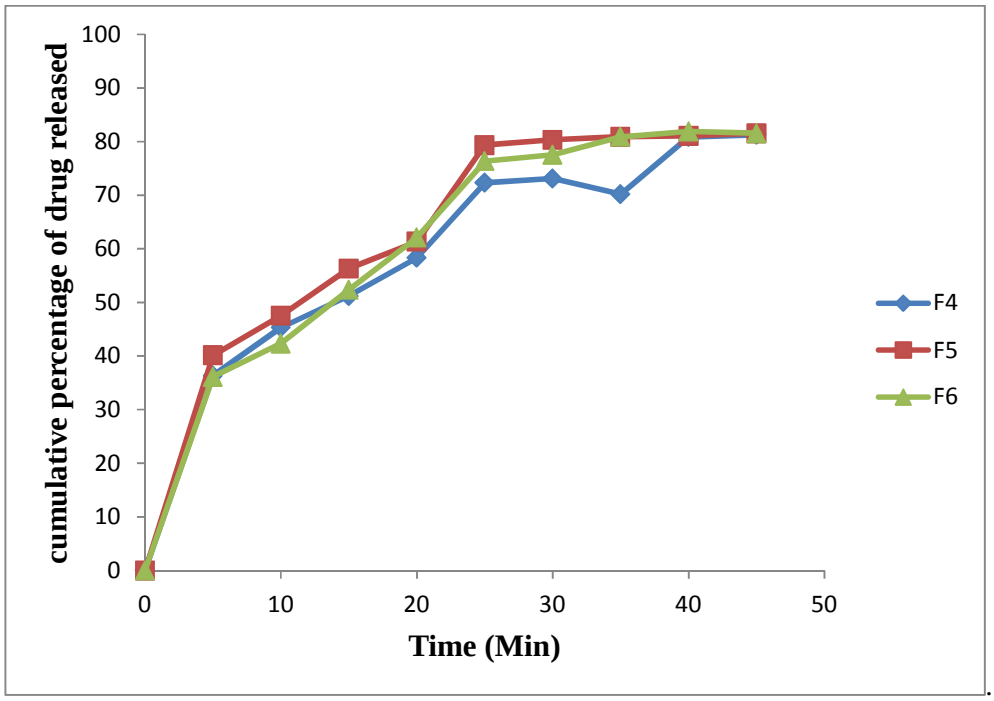


Fig 8. In-vitro drug release profiles of ODT of Nateglinide (F7-F9)

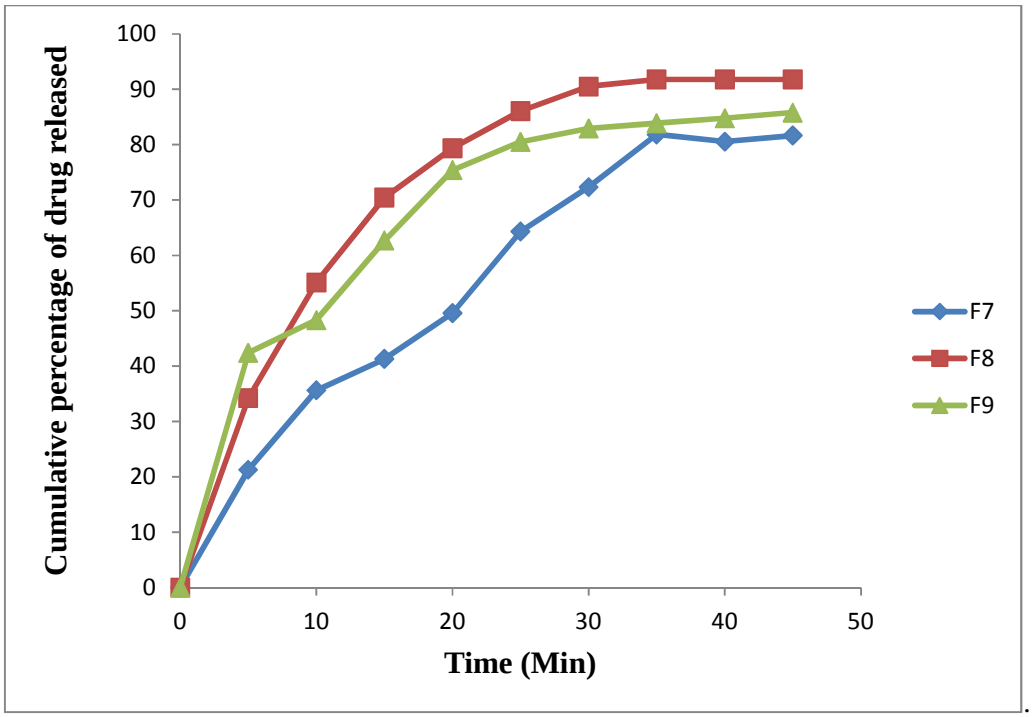


Fig 9. Comparison of In-vitro drug release profiles of ODT of Nateglinide (F1-F9)

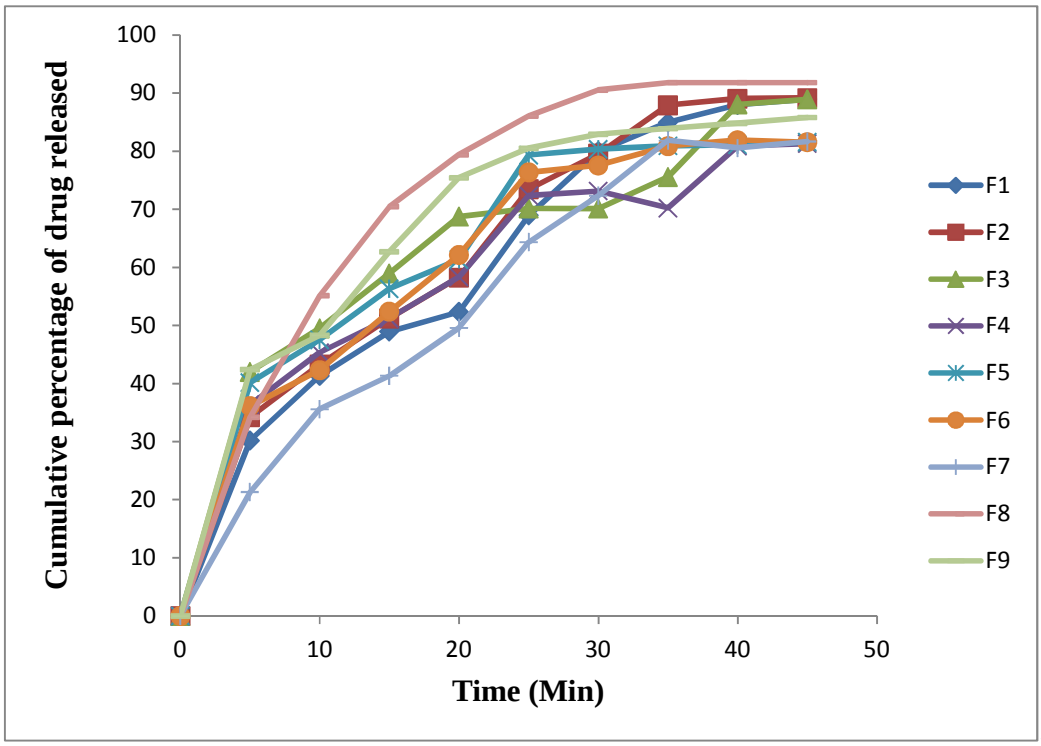
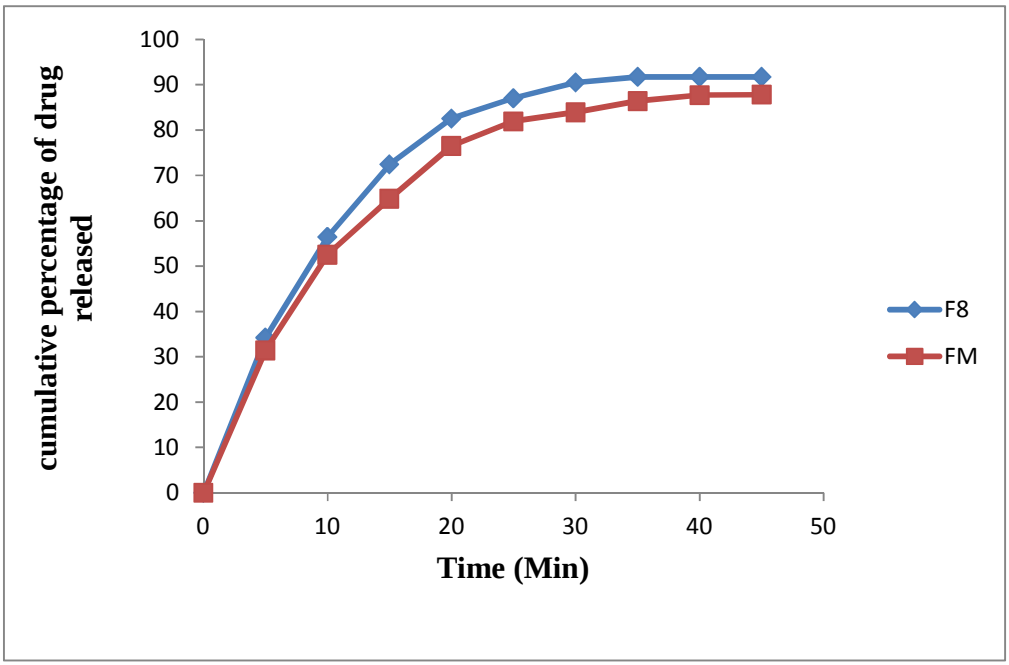


Table 5. Kinetics of in-vitro drug release ODT of Nateglinide

Formulation	First order release kinetics		Higuchi Constant Values		Korsymer-peppas	
	K Value	R^2 Value	K Value	R^2 value	n value	R^2 value
F1	1.039	0.8434	9.196	0.997	0.564	0.9698
F2	1.968	0.9212	9.844	0.993	0.508	0.9561
F3	1.975	0.8989	9.877	0.9902	0.498	0.9781
F4	1.991	0.9092	9.957	0.9868	0.492	0.9792
F5	1.949	0.9564	9.745	0.9964	0.489	0.9718
F6	1.022	0.9916	9.745	0.9925	0.51	0.9862
F7	1.065	0.9969	9.328	0.9969	0.494	0.9721
F8	1.947	0.9997	9.735	0.9992	0.483	0.9996
F9	1.993	0.9977	9.969	0.9978	0.476	0.9649

Fig 10. Comparitive in-vitro drug release profile of best formulation (F8) With marketed product



CONCLUSION

Suitable analytical method based on UV-Visible spectrophotometer was developed for Nateglinide. λ_{max} of 209 nm was identified by using phosphate buffer solution, pH 6.8 From the FT-IR spectra, the interference was verified and found that netaglinide did not interfere with the excipients used. Precompression studies of nateglinide were performed. Oral Disintegrating tablets of nateglinide were successfully prepared using crosscaramellose sodium, sodium starch glycolate and crospovidone by using direct compression method. Post compression parameters like general appearance, weight variation, hardness, friability, in-vitro dispersion and wetting time indicate that values were within permissible limit for all formulations. In-vitro drug release study was carried out and based on the results, F-8 formulation was identified as best amongst all the other formulations and its release was found to be 91.78% within 35 min. and it showed a constant release up to 45 min. The best formulation (F8) showed linearity when compared with marketed product. On the basis of the results, the formulation containing crospovidone was considered as ideal among all other formulations used for the development of nateglinide tablets.

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