Research Article

Design and *In vitro* Evaluation of Microporous Membrane Permeated Matrix Tablets of Nateglinide

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ABSTRACT

Oral route is the preferred route for the administration of drugs. Sustained release tablets retard the release of drugs such that its appearance in the systemic circulation is prolonged. Matrix systems are widely used for the purpose of sustained release. Matrix system is a system which prolongs and controls the release of the drug. Microporous membrane permeated technique is a type of technology in which the drug release is controlled by controlling the effective surface area by using a combination of gastrointestinal resistant polymer and gastrointestinal soluble material. Micro sized pores are formed upon the tablet due to dissolution of gastrointestinal soluble material. Nateglinide is an oral antihyperglycemic agent belonging to the class of meglitinides which act by binding to β cells of the pancreas to stimulate the release of insulin. The aim of the present study is to formulate matrix tablets of nateglinide by using Eudragit RS 100 and HPMC K 15M. Core tablets are tested for dissolution studies and the best formulation has been chosen for further studies. The optimized core tablet i.e. formulation NF4 is further coated with ethyl cellulose in which sodium lauryl sulphate was dispersed. The effect of compositions of core tablets and coating suspensions on the pharmaceutical characteristics was investigated *in vitro*. Among the prepared formulations, formulation MNG11 was the optimized formula.

Keywords: Nateglinide, HPMC K15M, Eudragit RS 100, Ethyl cellulose, Sodium lauryl sulphate, Matrix tablets.

INTRODUCTION

Diabetes mellitus commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. 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 channel on pancreatic beta-cells. The subsequent depolarization of the beta cell opens the calcium channel, producing calcium influx and insulin secretion.

The drug is widely used for the management of type-2 diabetes. It has short biological half-life of about 2 hours and bioavailability is 73%. Moreover, site of absorption of Nateglinide is in the intestine.[1-3]

The short biological half-life of the drug favors the development of sustained release formulation. 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 militating against success are very short half-life or a relatively large single dose, potent drug with a low margin safety, poorly soluble drug, and large first pass metabolism.

The recommended adult oral dosage of Nateglinide is 60 mg and 120 mg.[4-6]

The drug release in microporous membrane permeated matrix tablets is controlled by controlling the effective surface area by using a combination of gastro intestinal resistant polymer and gastro intestinal soluble material.

MATERIALS AND METHODS

Nateglinide was obtained as a gift sample from Jubilant Organosys, Delhi. Other ingredients were obtained from SD Fine Chemicals.

Preparation of the Core Tablets

Core tablets were prepared by employing drug, Eudragit RS 100, HPMC K 15 M, Microcrystalline cellulose, Pregelatinised starch, Aerosil and Talc. Quantities of all ingredients are tabulated in Table 1.

All the physical parameters (table 4) of the core tablets were found to be in the acceptable limits. Friability was less than 1%. Drug content ranged from 95.61% to 100.47%. All the tablets exhibited satisfactory hardness. Weight variation was within permissible limits. Based on the release studies formulation NF4 was optimized and was used for coating.

Coating of the Core Tablet

The core tablets of Nateglinide which has been optimised i.e NF4 were further coated with various rate controlling layers in order to have sufficient controlling of drug for

long term release. A total of 12 formulations were made. The tablets are coated by using Spray coating technique. The prepared coating solution has been filled in the sprayer. The tablets to be coated are placed in the pan. Coating solution is sprayed on to the bed in the rotating pan. Randomly tablets are taken and are checked for its weight increase. After attaining the desired weight the pan is stopped and the tablets are removed and used for the further analysis. Coating composition is given in Table 2.

Evaluation

Post compression Parameters

Post compression parameters were evaluated and they tabulated in Table 3.

Hardness[7-9]

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted.

Friability Test[7-9]

This test is performed in Roche friabilator and % friability was calculated as follows:

$$\% \, Friability = \frac{(W1 - W2)}{W1} \times 100$$

Where,

W1 = Initial weight, W2 = Final weight

Weight Variation Test[7-9]

To study weight variation individual weights of 20 tablets from each formulation were noted. Their average weight was calculated. Percent weight variation was calculated.

***In Vitro* Drug Release Studies**[10]

Dissolution of the core and coated tablets are performed by employing SGF for first two hours and later the dissolution is continued using SIF maintained at 37°C ± 0.5°C. At appropriate time intervals samples were extracted from the apparatus (each of 5 ml) and the content of the drug was analyzed by using UV/Visible spectrophotometer and absorbance was measured at 210 nm. Dilutions were performed as necessary using the dissolution medium. The extracted samples were replaced by 5 ml of fresh dissolution medium in an attempt to maintain sink conditions. The results were fitted into different kinetic models. Results were given in Table 4, 5.

Table 1: Composition of Core Tablets

Ingredients	NF1	NF2	NF3	NF4	NF5	NF6
Nateglinide	120	120	120	120	120	120
Eudragit S100	50	75	100	-	-	-
HPMC K 15 M	-	-	-	50	75	100
Microcrystalline Cellulose	70	45	20	70	45	20
Pregelatinised Starch	50	50	50	50	50	50
Aerosil	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total Weight	300mg	300mg	300mg	300mg	300mg	300mg

Table 2: Ingredients of Coating Solution

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12
Ethyl cellulose	15	15	15	15	10	10	10	10	5	5	5	5
Sodium lauryl sulphate	0.5	1.0	1.5	2.0	0.5	1.0	1.5	2.0	0.5	1.0	1.5	2.0
Titanium Di Oxide	2	2	2	2	2	2	2	2	2	2	2	2
Castor Oil	2	2	2	2	2	2	2	2	2	2	2	2
Methanol	q.s	q.s	q.s.	q.s.	q.s.	q.s.	q.s	q.s	q.s.	q.s.	q.s.	q.s.

*All the ingredients mentioned above are in the terms of "percentages."

Table 3: Post Compression Parameters of the Core Tablet

Parameter	NF1	NF2	NF3	NF4	NF5	NF6
Weight Variation (g)	0.301±0.02	0.291±0.12	0.304±0.009	0.303±0.02	0.299±0.01	0.302±0.031
Drug Content (%)	98.15±0.56	99.15±0.92	95.61±0.28	97.15±0.09	100.47±0.70	99.85±0.21
Hardness (Kg/cm^2)	5.9±0.3	5.8±0.2	6.1±0.4	5±0.2	5.9±0.1	6.3±0.2
Friability (%)	0.56±0.025	0.66±0.034	0.65±0.021	0.62±0.013	0.58±0.012	0.54±0.012

Table 4: Dissolution Data of the Core Tablet Formulations

Time (min)	Cumulative Drug Release					
	NF1	NF2	NF3	NF4	NF5	NF6
0	0	0	0	0	0	0
5	39.73	27.69	19.56	15.39	11.39	16.95
15	57.69	50.39	29.32	30.76	26.77	32.46
30	81.76	74.69	37.54	45.69	39.57	47.39
60	98.69	93.67	49.69	62.59	47.69	59.47
90	-	97.49	62.49	76.39	59.69	68.89
120	-	-	78.69	93.59	76.38	75.69

Table 5: Dissolution Data for Coated Tablet Formulations

	Cumulative Drug Release (%)											
Time (hr)	MNG1	MNG2	MNG3	MNG4	MNG5	MNG6	MNG7	MNG8	MNG9	MNG10	MNG11	MNG12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	0.11	0.53	0.91	1.59	1.65	1.05	1.92	2.54	2.88	4.17	11.54	14.65
1	0.21	0.81	1.08	3.01	1.91	2.55	3.87	3.65	4.87	7.93	16.87	19.71
2	0.35	1.21	1.87	5.16	4.29	5.18	6.46	7.91	10.54	13.78	21.68	27.65
4	0.49	1.94	2.87	6.93	7.38	8.42	9.56	10.65	15.66	24.56	28.38	38.91
6	0.61	3.65	4.14	8.48	9.1	10.41	12.36	14.51	19.85	30.19	34.55	48.65
8	0.75	4.91	6.57	10.59	12.22	11.49	13.22	17.43	24.67	36.56	43.59	54.65
10	0.89	5.88	8.98	12.86	15.37	14.85	15.54	21.56	29.56	41.74	55.22	63.75
12	1.05	7.43	11.49	11.56	17.43	18.22	17.19	29.07	33.65	50.09	59.19	77.81
14	1.49	9.48	15.75	12.86	20.98	19.55	22.87	33.95	39.81	58.71	64.65	85.13
16	1.65	11.31	19.44	15.81	26.54	24.16	27.94	39.76	46.56	64.65	71.85	94.88
18	1.98	12.59	21.43	18.24	31.59	31.59	32.88	46.54	51.32	73.99	82.19	99.13
20	2.99	17.48	24.56	21.15	34.74	39.74	41.56	53.71	58.75	79.85	93.65	99.01
22	3.54	23.88	29.19	29.32	36.33	43.21	50.85	58.11	63.21	84.61	96.59	98.65
24	5.91	27.91	31.15	35.56	41.65	52.65	59.67	66.15	70.11	89.91	99.14	98.91

RESULTS AND DISCUSSION

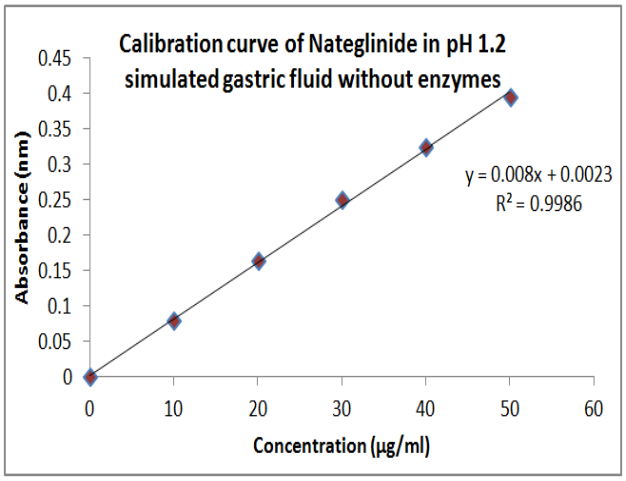

Figure 1: Standard Curve in pH 1.2 SGF

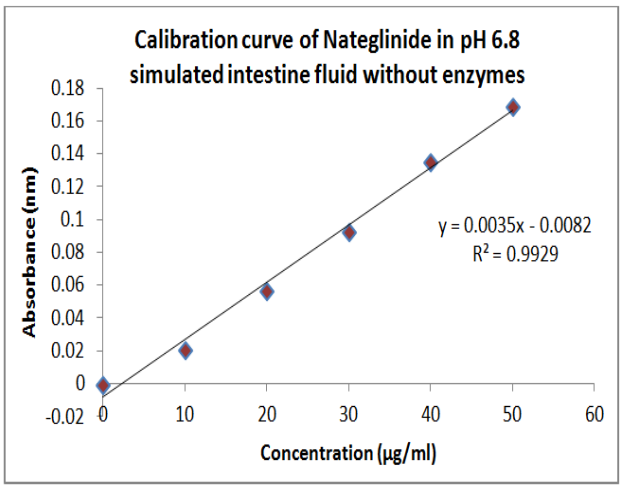

Figure 2: Standard Curve in pH 6.8 SIF

Figure 3: Nateglinide Coated Tablet

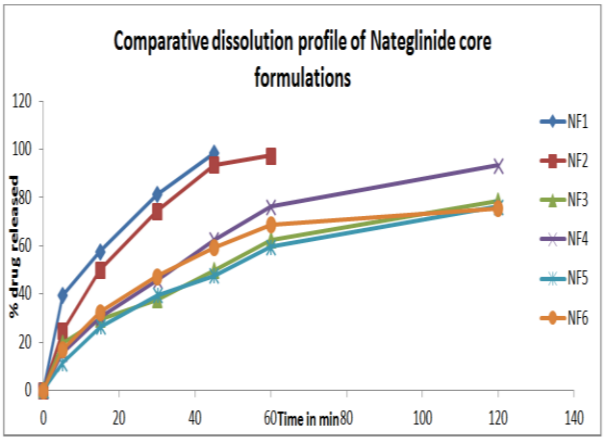

Figure 4: Dissolution Graph of Nateglinide Core Tablets

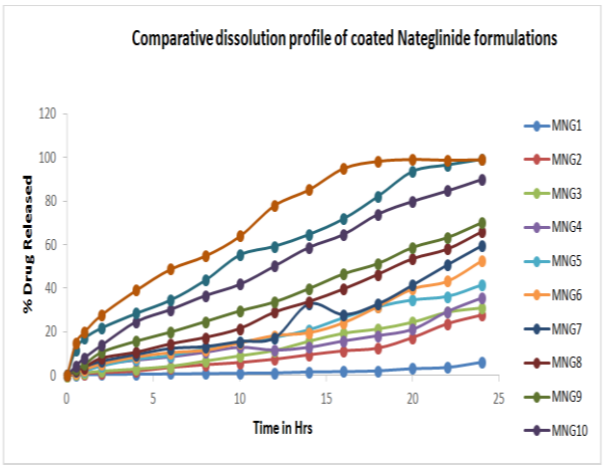

Figure 5: Dissolution Graph of Coated Nateglinide Tablets

CONCLUSION

The objective of the present study is to sufficiently control the release of an antidiabetic drug nateglinide. Matrix tablets of nateglinide were prepared by using Eudragit RS 100 and HPMC K 15M. Based on the dissolution of core tablets formulation NF6 was optimized and selected for coating. Different formulations were developed by employing microporous permeation method using Ethyl cellulose and Sodium lauryl sulphate. The effect of coating composition on drug release was evaluated.

Among the various formulations prepared, formulation MNG11 was optimized. Hence it can be concluded that microporous membrane permeated matrix tablets of nateglinide can sustain the drug release over a prolonged period of time.

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