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Development and Evaluation of gastroretentive matrix tablets of Nateglinide

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ABSTRACT

Nateglinide is used in the treatment of generalized non insulin dependent diabetes mellitus. Once inside the cell, glucose is metabolized to produce ATP. High concentrations of ATP inhibit ATP-sensitive potassium channels causing membrane depolarization. When extracellular glucose concentrations are low, it causes repolarization. The influx of calcium ions stimulates calcium-dependent exocytosis of insulin granules. Nateglinide increases insulin release by inhibiting ATP-sensitive potassium channels in a glucose-dependent manner. The F4 formulation diffusion exponent n value is in between 1.07 to1.99. F4 gave better-controlled drug release and floating properties in comparison to the other formulations. The release pattern of the F4 formulations was best fitted to Korsmeyer-Peppas model, Higuchi and first-order model. The most probable mechanism for the drug release pattern from the formulation was non-Fickian diffusion or anomalous diffusion.

Keywords: Non-insulin dependent diabetes mellitus.

INTRODUCTION

Oral route has been one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage forms [1]. For many decades treatment of an acute disease or chronic illness has mostly accomplished by delivery of drugs to patients using conventional drug delivery system [2-4]. Conventional oral drug products are formulated to release the active principle immediately after oral administration to obtain rapid and complete systemic drug absorption [5-6]. Examples such as griseofulvin, digoxin, phenytoin, sulphathiazole & chloramphenicol come immediately to mind [7-8]. Consideration of the modified Noyes – Whitney equation provides hints for dissolution improvement. Nateglinide having the high solubility in the stomach region and it is having better absorption from the upper GIT, hence the model drug has been selected to convert into gastro retentive floating tablet with a view to increase its oral bioavailability [9-10].

$$\frac{dc}{dt} = \frac{AD(C_S - C)}{h}$$

AIM AND OBJECTIVES

1. The aim of the present study is to achieve prolonged retention of the dosage form in the stomach for a time period of 12hrs.
2. The primary objective was to formulate and evaluate gastro retentive floating tablets of the nateglinide by using different polymers such as Carbopol and Xanthan gum in different ratios by employing Wet granulation method.

MATERIALS AND METHODOLOGY

Table 1: Ingredients used in this study

Ingredients	Supplier
Xanthan gum	Supplied By Pharma Train
HPMC K100M	SD Fine Chemicals, Mumbai
HPMC K15M	SD Fine Chemicals, Mumbai
Carbopol	SD Fine Chemicals, Mumbai
MCC	FMC Bio Polymer, Mumbai
PVP K 30	SD Fine Chemicals, Mumbai
Talc	SD Fine Chemicals, Mumbai
Magnesium Stearate	SD Fine Chemicals, Mumbai

Table 2: Equipments used in this study

Name of the Equipment	Model
Electronic weighing balance	Scale-Tec
Friabilator	Roche FriabilatorElectrolab, Mumbai
Laboratory oven	Dtc-00r
Compression machine	Cmd (Cadmach)
Tablet hardness tester	Pfizer Hardness Tester, Mumbai
UV	LabindiaUv 3000+
Dissolution apparatus	Electrolab TDT-08L
Verniercallipers	Cd-6”Cs

Table 3: Formulation of nateglinide floating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nateglinide powder (1:4)	50	50	50	50	50	50	50	50	50
Xanthan gum	40	80	-	-	-	-	-	-	-
HPMC K 100 M	-	-	40	80	-	-	-	-	-
HPMC K15 M	-	-	-	-	40	80	-	-	-
Carbopol	-	-	-	-	-	-	40	80	-
MCC	125	135	125	135	125	135	125	135	125
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Megnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

RESULTS AND DISCUSION

Calibration curve of nateglinide in 0.1N HCL solution

Table 4: Calibration graph values of Nateglinide in 6.8 phosphate buffer at 217 nm

Concentration (µg/mL)	Absorbance
0	0.000
1	0.051
2	0.096
3	0.139
4	0.182
5	0.225

Inference

The standard calibration curve of Nateglinide in 0.1N HCL showed good correlation with regression value of 0.999.

Table 5: Pre compression studies of nateglinide floating tablets *n=3

Formulation Code	Bulk density (kg/cm^3)	Tapped density (kg/cm^3)	Cars index	Hausner's ratio	Angle of repose (˚)
F1	0.43	0.52	17.3	1.41	25.62
F2	0.40	0.46	13.0	1.5	31.29
F3	0.50	0.58	13	1.16	29.58
F4	0.44	0.51	13.7	1.25	26.29
F5	0.39	0.47	17.0	1.56	25.23
F6	0.42	0.52	19.2	1.45	25.24
F7	0.36	0.39	7.6	1.0	28.03
F8	0.41	0.50	18	1.5	24.4
F9	0.38	0.42	7.8	1.3	29.05

The nateglinide floating tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table. The bulk density and the tapped density for all formulations were found to be almost are not similar. The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 13and 19.2 respectively, indicating good flow and compressibility of the blends. The angle of repose for all the formulations was found to be in the range of 24-31 which indicating passable flow.

Table 6: Post compression studies

Formulation Code	% weight variation	Thickness (mm)	% friability	% Drug Content	Hardness (Kg/cm^2)
F1	250.27	3.56±0.11	0.22	102.0 ±1.1	4.98 ±0.17
F2	250.16	4.23±0.15	0.15	101.3 ±1.5	5.13 ±0.15
F3	251.34	3.43±0.057	0.12	99.8±1.3	4.95 ±0.13
F4	253.76	4.38±0.12	0.43	101.7 ±0.8	4.88 ±0.04
F5	252.28	3.48±0.05	0.32	100.6±1.2	4.93 ±0.05

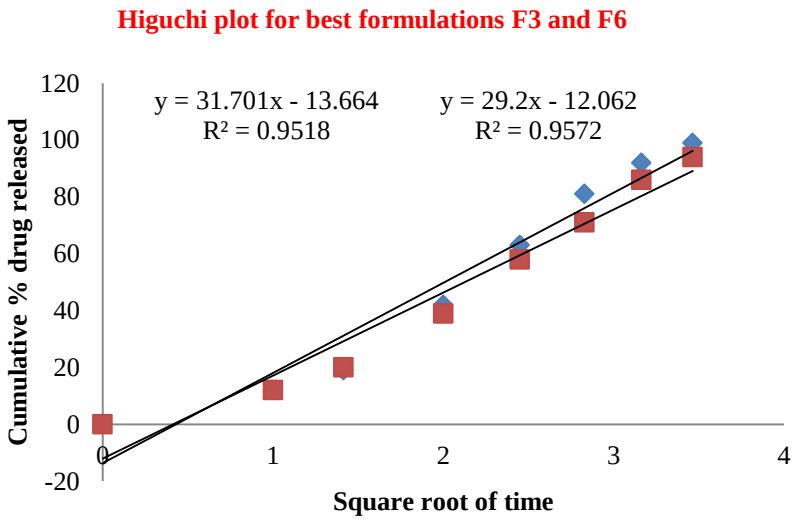
F6	253.45	4.32±0.15	0.14	98.9 ±2.1	5.02 ±0.02
F7	251.43	3.52±0.05	0.20	99.2± 1.7	4.87 ±0.10
F8	250.72	4.26±0.11	0.33	99.5± 1.4	4.93±0.05

The variation in weight was within the limit. The thickness of tablets was found to be between 3.43 to4.48mm.The hardness for different formulations was found to be between 4.88-5.13kg/cm^2, indicating satisfactory mechanical strength. The friability was < 1.0% W/W for all the formulations, the drug content was found to be within limits 99.81to 100.34 %.

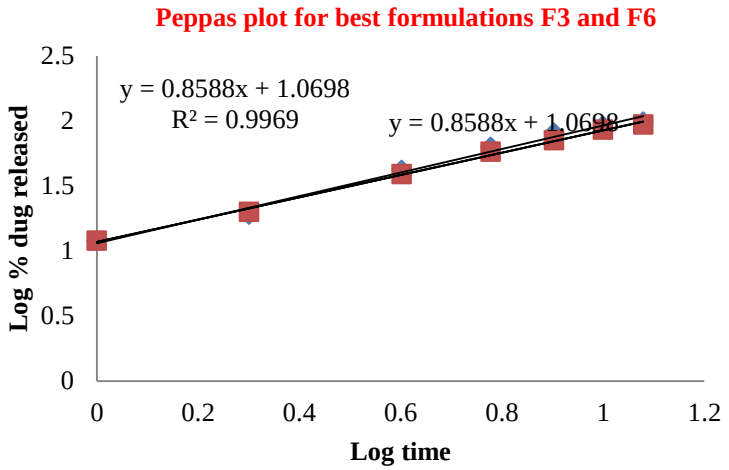
Table 7: in vitro buoyancy studies of nateglinide floating tablets

Formulation Code	Floating lag time (sec) n = 3	Total floating time (h) n = 3	Matrix Integrity up to 12hrs n = 3
F1	20	12.8	+
F2	36	12.7	+
F3	35	12.6	+
F4	24	12.8	+
F5	40	12.9	+
F6	80	12.4	+
F7	20	12.6	-
F8	20	12.8	+

Higuchi plot for best formulation F3 and f6



Peppas plot for best formulation f3 and f6



Among the different control release polymers Eudragit RL100 was showing highest drug release retarding capacity**.**F4 was showing the satisfactory results and it was having better sustainability when we plot the release rate kinetics for best formulation F3 and f6was following first order because correlation coefficient value of first order is more than zero order 2 value.

SUMMARY AND CONCLUSION

From the experimental data, it can be concluded that floating tablets of nateglinide formulated to increase gastric residence time and thereby improve its therapeutic efficacy. Carbopol was respectively showed better Sustained drug release of nateglinide. Synthetic polymers was showing more rate retarding drug release and matrix integrity, the order of better controlled release polymers are Carbopol>xanthum gum. When drug: polymer concentration increases the release rate decreases this is because of reason when the concentration of polymer increases the diffusion path length increases. Formulated tablets showed satisfactory results for various Post compression evaluation parameters like: tablet thickness, hardness, weight variation, floating lag time, total floating time, content uniformity and *in vitro* drug release. Formulation F4 gave better-controlled drug release and floating properties in comparison to the other formulations. The release pattern of the F4 formulations was best fitted to Korsmeyer-Peppas model, Higuchi and first-order model. The most probable mechanism for the drug release pattern from the formulation was non-Fickian diffusion or anomalous diffusion.

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