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FORMULATION AND EVALUATION OF BILAYER TABLET OF NATEGLINIDE

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ABSTRACT

The main objective of research work is to develop a bilayer tablet of Nateglinide, in which one layer is immediate layer for immediate action and second layer is the sustain release layer for maintaining the dose of the drug. Preformulation study was performing for various parameters like melting point, Bulk density, Tapped density. Carr's index, Housner ratio etc. Bilayer tablets were prepared in two stages by using Crosspovidone different viscosity grades of hydroxy propyl methyl cellulose (HPMC) viz., K4M and K100M. The prepared Bilayer tablets were evaluated for hardness, bulk density, tapped density, friability, uniformity of weight, drug content, in vitro dissolution and drug-polymer interaction. Immediate layer drug content result was found to be 4.89±0.152 kg/cm2 and 99.26 ±1.42. On the basis of disintegration and dissolution studies, I 3 was found to be superior amongst them which show disintegration time 28 ±2.10 second and 98% drug release and sustain layer drug content result was found for S3 5.4 ±0.31 kg/cm2and 97.86 ±0.90, for S6 5.5±0.52 kg/cm2 and 97.55±1.59 and for S9 5.5±0.15 kg/cm2 and 98.25±1.53 respectively, but for further refinement the batches were subjected for dissolution studies. On the basis of dissolution studies, the S9 batch was found to be superior amongst them which show 95 % drug release in 24 hours.

KEYWORDS: Nateglinide, disintegration, immediate layer, Sustain Release, Hydroxy propyl Methyl cellulose.

INTRODUCTION

The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the of action, reducing the dose required or providing uniform drug delivery. The primary objective of sustained release drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. Bi- layer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose.

Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems.

MATERIALS AND METHODS

Material

Nateglinide was obtained as gift- sample from Glenmark Pharmaceuticals Limited Mumbai and carbopol 934, HPMC of pharmaceutical grade were procured from PBRI, Bhopal and liquid paraffin, Span 80, ethanol, acetone procured from SD Fine chemicals.

Pre-formulation studies

Pre- formulation is considered as important phase where researcher characterizes the physical and chemical properties of drug substance which helps to develop stable, effective and safe dosage forms and also check possible interaction with various excipients.

Identification by UV

Identification and authentication of drug sample was also done by ultraviolet spectroscopy and it was scanned in the range of 200-400 mm. Drug absorption maximum was found to be at 212 nm as per specification and this result indicates the purity of the drug.

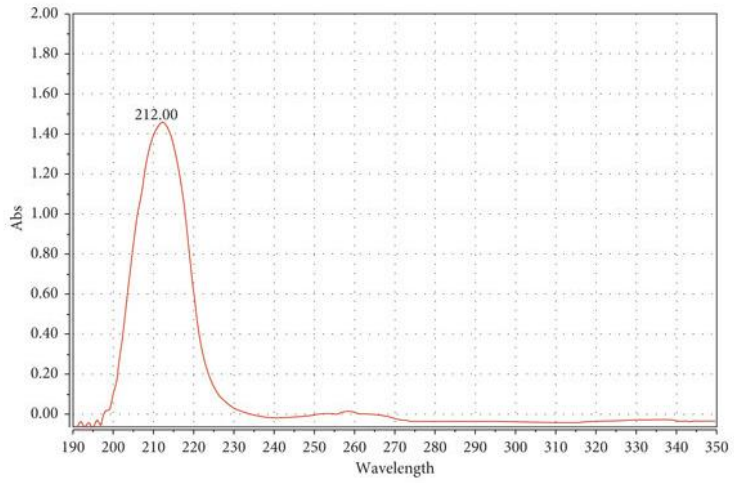

Figure No. 1: UV spectra of the sample drug.

Formulation of Nateglinide bilayer tablet

The controlled release limited by solubility was precluded and delivery of active material form the preparation was controlled by the formulation. All formulation were prepared in bilayer foam in which first layer is 'immediate release layer' consist of Crosspovidone which is super disintegrate which provide fast release of active material and the second layer 'sustained release layer' consist of HPMC provided controlled release of active material.

In the present study, hydrodynamically balanced systems of Nateglinide were prepared by using different viscosity grades of hydroxy propyl methyl cellulose (HPMC) viz., K4M and K100M. The prepared Bilayer tablets were evaluated for hardness, bulk density, tapped density, friability, uniformity of weight, drug content, in vitro dissolution and drug-polymer interaction. Formula given below in table No. 1.

Table No. 1: Formulation of Compressed Nateglinide Bilayer Tablet.

S. No.	Formula (In mg)	Formula for Bilayer tablet	
		I 3	S 9
1	Nateglinide	20	40
2	Crosspovidone	10	-
3	Mannitol	86	15
4	Magnesium stearate	1.42	1.42
5	HPMC (K4M)	-	150
6	HPMC (K100M)	-	100
7	Talc	2.85	2.85

Compatibility Study FT-IR Spectra Analysis

FT-IR Spectroscopy can be used to investigate and predict any physicochemical interactions between different components in a formulation. While selecting the ingredients, we would choose those which are stable, compatible and therapeutically acceptable.

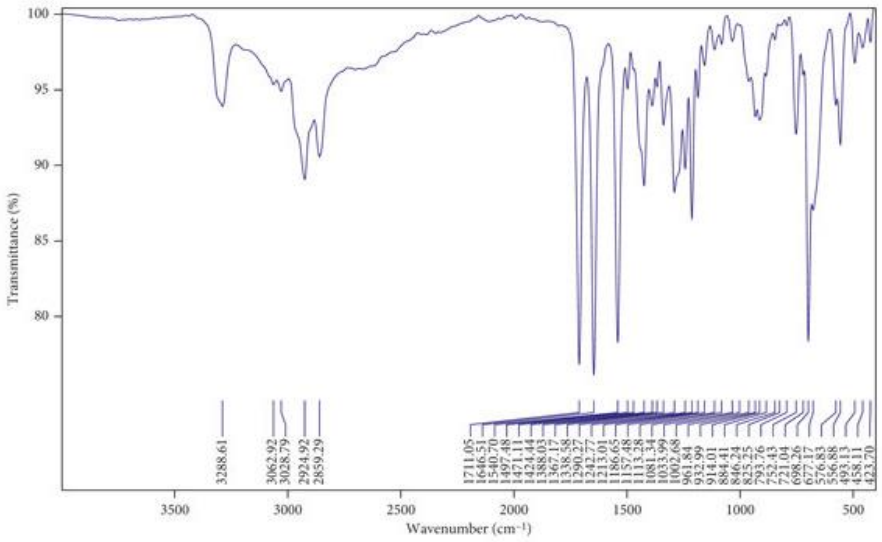

Figure No. 2 Infra red characteristics of Nateglinide drug sample

S. No.	Wave no.(cm^{-1})	Interpretations
1.	3265	N-H Stretching
2.	2940	C-H Stretching of Alkynes
3.	1680	Alcoholic C-O Stretching
4.	1635	C=O Stretching
5.	1560	Alkanes (C-C Stretching)

RESULT

Formulation of Nateglinide Immediate Release Layer

Immediate release layers Nateglinide were prepared using -factorial design by taking variable concentrations of Crosspovidone at three levels. I 1, I 2, I 3 are formulation code of different formulation.

Table No. 2: Composition of Nateglinide Immediate Release Layer.

Ingredient(mg)	I1	I2	I3
Nateglinide	20	20	20
Crosspovidone	2	5	10
Mannitol	94	91	86
Magnesium stearate	1.42	1.42	1.42
Talc	2.85	2.85	2.85

Formulation of Nateglinide Sustained Release Layer

Sustained release layers of Nateglinide were prepared using -factorial design by taking variable concentrations of HPMC K4M and HPMC K100M at three levels. S1, S2, S3, S4, S5, S6, S7, S8, S9 are formulation code of different formulation.

Table No. 3: Composition of Nateglinide Sustained release layer.

Ingredient (mg)	S1	S2	S3	S4	S5	S6	S7	S8	S9
Nateglinide	40	40	40	40	40	40	40	40	40
HPMC (K4M)	100	100	100	125	125	125	150	150	150
HPMC K100M	60	80	100	60	80	100	60	80	100
Mannitol	95	75	55	75	55	35	55	35	15
Magnesium stearate	1.42	1.42	1.42	1.42	1.42	1.42	1.42	1.42	1.42
Talc (mg)	2.85	2.85	2.85	2.85	2.85	2.85	2.85	2.85	2.85

Evaluation of Prepared Compressed Nateglinide Bilayer Tablet

The Nateglinide Bilayer Tablet evaluation was on following parameter like Friability, Hardness, Disintegration time, Weight variation, % Drug Content, in vitro % drug release results given below:

Table No. 4: Evaluation of Nateglinide Immediate Release Layer.

Batch	% Friability	Hardness (Kg/cm2)	Disintegration time (Sec.)	Weight variation	% Drug Content
I1	0.74 ±0.031	4.94±0.0312	42 ±2.51	120.0 ±0.270	97.12 ±0.69
I2	0 .79 ±0.022	5.01±0.022	35 ±3.19	120.1 ±0.170	97.86 ±1.21
I3	0.83 ±0.059	4.89±0.152	28 ±2.10	120.2 ±0.070	99.26 ±1.42

Table No 5: Evaluation of Nateglinide Sustained Release Layer.

Batch	% Friability	Hardness (Kg/cm2)	Disintegration time (Sec.)	Weight variation	% Drug Content
S1	0.64 ±0.053	5.0± 0.41	142 ±2.41	297.2 ±2.070	93.32 ±0.54
S2	0.65 ±0.041	4.9 ± 0.41	249 ±2.23	298.2 ±1.070	95.26 ±0.62
S3	0.70 ±0.033	5.4 ± 0.31	294 ±2.59	298.6 ±0.670	97.86 ±0.90
S4	0.74 ±0.039	4.7 ± 0.39	347 ±3.20	298.5 ±0.770	95.25 ±1.23
S5	0.75 ±0.051	4.9 ± 0.51	397 ± 3.51	297.5 ±1.730	96.76 ±1.76
S6	0.79 ±0.052	5.5 ± 0.52	439 ±2.52	297.7 ±1.600	97.55 ±1.59
S7	0.81 ±0.029	5.4 ± 0.29	488 ±3.29	298.5 ±0.700	97.23 ±1.79
S8	0.82 ±0.055	5.5 ± 0.21	555 ±2.21	298.6 ±0.600	97.43 ±1.85
S9	0.87 ±0.059	5.5± 0.15	567 ±2.15	298.8 ±0.500	98.23 ±1.53

In vitro drug release of Compressed Nateglinide Bilayer Tablet

The dissolution medium consisted of 500ml of 0.1NHCL. The release was performed at 37oC ± 0.5oC, with a rotation speed of 50 rpm. The slide was placed in to the bottom of the dissolution vessel. Samples (5 ml) were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through filter paper and analyzed after appropriate dilution by UV spectrophotometer at 212 nm. The concentrations of Nateglinide in samples were determined by the proposed UV absorbance method.

Table No 6: In-Vitro dissolution studies of immediate release layer.

S. No.	Time(min.)	% Drug release I 1	% Drug release I 2	% Drug release I 3
1	0	0	0	0
2	5	15	25	32
3	10	42	62	73
4	15	66	78	84
5	20	79	87	94
6	25	85	92	96
7	30	92	96	98

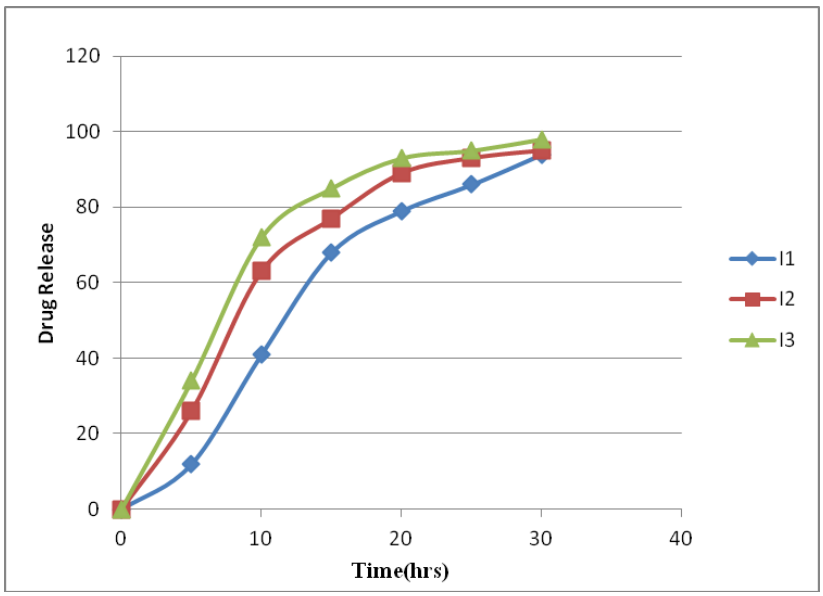

Figure 3: Cumulative % drug release of immediate release of Nateglinide I1, I2, I3

Table No 7: In-Vitro dissolution studies of sustained release layer.

S. No.	Time (In hrs.)	% Drug Release								
		S1	S2	S3	S4	S5	S6	S7	S8	S9
1	0	0	0	0	0	0	0	0	0	0
2	1	15	14	12	11	10	9	9	8	8
3	2	30	28	27	25	24	23	21	21	18
4	6	55	52	49	46	43	39	36	33	30
5	10	75	73	70	67	63	60	57	53	50
6	15	80	78	75	73	70	65	62	60	57
7	18	95	95	93	90	85	82	78	75	73
8	24	97	98	97	98	98	97	98	97	95

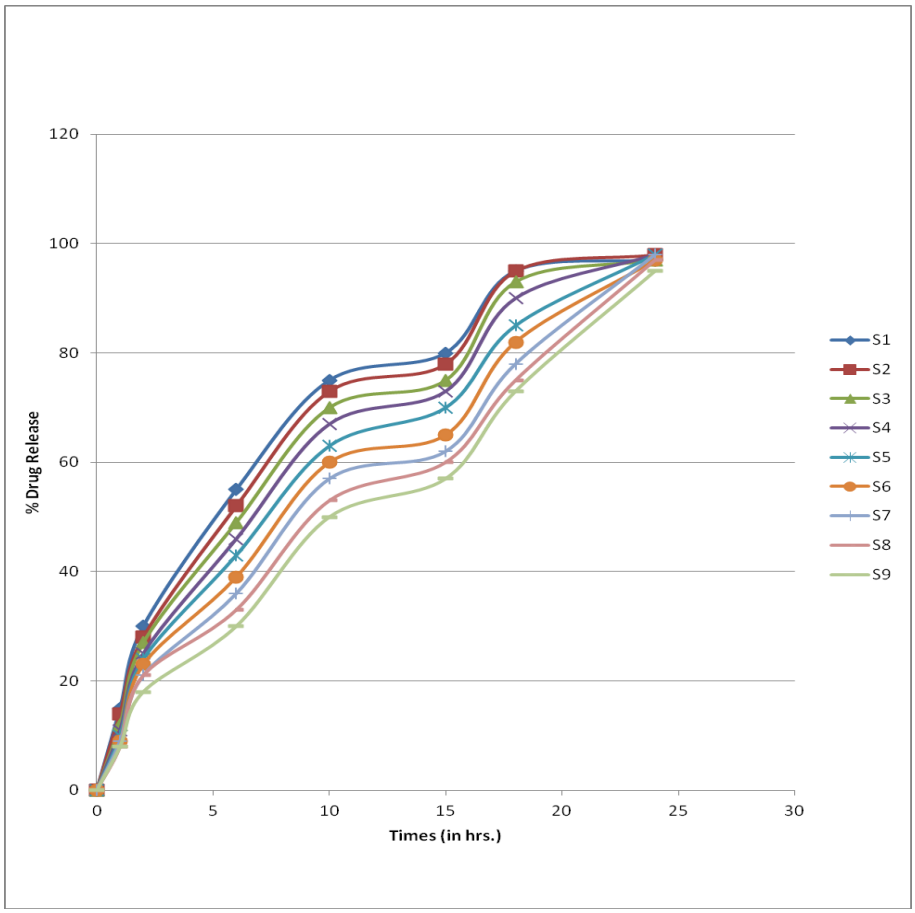

Figure 4: Cumulative % drug release of sustained release layer of Nateglinide S1 to S9.

CONCLUSION

The present study demonstrated the successful preparation of once daily conventional release bilayer tablet of Nateglinide. The project work entitled, formulation development, and optimization of Nateglinide bilayer tablet was carried out in the present study it was mainly concentrated on the optimization of the formulation based on compatibility study with IR as well as some other parameters. The Optimized formulation I3 and S9 was studied for the drug content and in-vitro drug release. Tablet blends were evaluated for various parameters such as bulk density, tapped density, and tablets were evaluated for thickness, drug content, hardness, and weight variation.

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