Available online on 15.09.2015 at http://jddtonline.info
Journal of Drug Delivery and Therapeutics
Open access to Pharmaceutical and Medical research

RESEARCH ARTICLE

FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF NATEGLINIDE

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Received 04 Aug 2015; Review Completed 25 Aug 2015; Accepted 26 August 2015, Available online 15 Sep 2015

ABSTRACT

The objective of this work was to prepare and evaluate oral sustained release matrix tablet of Nateglinide and to study the effect of proportion of wax and addition of release liner on *in-vitro* release of drug.The prepared tablets were evaluated for pre and post compression parameters. Stability study of the promising formulation was also performed. The matrix tablets were prepared by Direct compression, Co-processed & melt granulation, method using wax in concentration 25%, 35% & 45% and evaluated for on *in-vitro* drug release using Compritol & Precirol. No interactions were found between drug and excipients. Formulation containing 25% Precirol F13 shows releases up to 12 hours. Tablets with release characteristics offers critical advantages such as site specificity with improved absorption and efficacy etc.

Keywords: Nateglinide, Sustained release, Compritol 888, Precirol ATO 5, Melt Granulation, Direct compression, Co-processing

INTRODUCTION

A sustained-release dosage form is defined as "any drug or dosage form modification thatprolongs the therapeutic activity of the drug" [1]. Development of oral sustained release (SR) tablets of highly water soluble drugs or bioactives has always been a challenge and therefore, opportunity for formulation scientist. Most of these drugs if not formulated properly, may be released at a faster rate resulting in exceeding the maximum therapeutic levels and hence will lead to toxic side effects. Sustained delivery of such drugs ensures improved drug delivery and patient compliance, greater safety and efficacy, desired release kinetics and helps in maintaining the plasma drug concentration within the therapeutic window for extended period of time [2, 3]. Lipids like glycerides are a family of excipients which have generated considerable interest in the preparation of oral dosage forms. Some glycerides such as Compritol ATO 888 (glyceryl behenate), Precirol ATO 5 (glyceryl palmitostearate) can be used for the preparation of sustained release dosageforms [5]. The esterification of glycerol by long chain fatty acid gives them a pronounced hydrophobic character with a low HLB value of 2 [6]. Several techniques including melt granulation [7], melt pelletization [8], hot melt extrusion [9] and hot melt coating [10] have been used to obtain sustained release dosage forms from glycerides-based formulations.

Melt granulation (MG) is a solvent-free process which involves the use of a substance that melts at a relatively low temperature. This substance can be added in the molten form over the substrate or in the solid form, which is then heated above its melting point. The substance acts as a liquid binding agent, and the technique does not require the use of organic solvents. Moreover, in melt granulation drying is not necessary and thus, the process is less consuming in terms of time and energy compared to other methods [4]. Sustained release matrix tablets have been produced with Compritol ATO 888 & Precirolby various methods including MG[11], Co-processing and direct compression (DC)[12].

Nateglinide, *N*-(trans-4-isopropylcyclohexylcarbonyl)-D-phenylalanine] is a phenylalanine derivative lackingeither a sulfonylurea or benzamido moiety, which can restore the physical insulin secretion pattern lost in type 2 diabetes mellitus patients with postprandial hyperglycemia. Pharmacologically, nateglinide reportedly acts on pancreatic cells via the closure of the adenosine triphosphate–sensitive potassium channels by binding to sulphonylurea receptor subunits causingcell depolarization, calcium influx, and insulin release.The drug has a rapidonset and short duration of insulinotropic action (t½ is _1.5 hours and Tmax is_0.5–1.0 hour after dosing).[13,14]

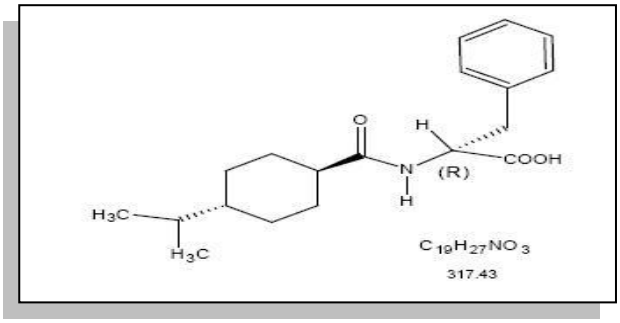

Figure 1: Nateglinide structure

MATERIALS AND METHODS

Materials

Nateglinide was a gift from Pure chem, Bharuch, India while Compritol ATO 888 and Precirolwere obtained free of charge from Gattefosse SAS India. Di-Calcium phosphate, magnesium stearate, Aerosil 200, concentrated hydrochloric acid, sodium hydroxide and potassium dihydrogen phosphate were purchased from SD Fine chemicals, Mumbai, India. Distilled water (D.W.)was prepared freshly whenever required. Other chemicals and reagents used were of analytical grade.

Methods

Preparation of Nateglinide matrix tablets

Preparation of wax matrix tablets was done by three methods: Melt granulation, Co-processing and Direct compression as follows.

Identification of drug:

The obtained sample was examined by infrared absorption spectral analysis and was compared with the reference standard IR spectrum of API. Also UV spectrum was taken to identify the compound based on λ_{max} and peak shape.

Organoleptic characteristics:

The color, odour and taste of the drug were characterized and recorded using descriptive terminology.

Solubility of drug:

The solubility of Drug was determined as per BCS. The solubility was checked in 250 ml of 0.01N HCl with 0.5% SLS and buffers within pH range 2 – 8. The highest amount of dose was accurately weighed and transferred in individual volumetric flask containing different solutions and sonicate for 30 minutes. Interpretation was done based on BCS classification which states that drug is BCS class II.

Pre compression parameters :

a) **Angle of repose** : Angle of repose of the granules will be measured by the fixed height method.

$\theta = \tan^{-1} h/_r\theta$ = Angle of repose

h = Height of powder heap

r = Radius of the powder cone

b) **Bulk density :** The powder sample equivalent to 10g will be accurately weighed, will fill in a 50 ml graduated cylinder, the powder will be levelled & the unsettled volume (Vi) will be noted. The bulk density will be calculated in g/cm3 by the formula.

$\rho_i = m / V_i$ m = mass of the blend

V_i = untapped volume

c) **Tapped density** :

$\rho_t = m/V_t$ V_t is tapped volume

d) **Hausner's Ratio :** It is measurement of frictional resistance of the drug .The ideal range should be 1.2-1.5. It will be determined by the ratio of tapped density and bulk density.

Tapped density/bulk density

e) **Carr's index :** Based on the bulk density & tapped density, the percentage compressibility of the granules will be computed using the Carr's compressibility index by the formula,

(Tapped density-bulk density)*100/Tapped density

Post compression parameters:

a) **Weight Variation :** Will be done as per USP

b) **Thickness :** Will be Measured by Vernier Calipers

c) **Hardness :** Will be Measured by Monsanto Hardness Tester

d) **Friability :** Will be Measured by Roche friabilator

%Friability = $(W_1-W_2/W_2)*100$

W_1= weight of tablets before test

W_2= weight of tablets after test

e) In-Vitro dissolution study:

An *in-vitro* dissolution study will be carried out in

- Dissolution medium: 0.5% sodium lauryl sulphate (SLS) in 900 ml of Phosphate buffer (pH 6.8) with type II paddle.
- Temperature: 37±0.5°C
- Stirring speed of Paddle:50rpm
- Time Point(hr): 1,2,3,4,5,6,7,8,9,10,11,12
- Sample amount: 5ml
- Volume: 900ml

Method of preparation:

Melt granulation method: The waxes(Compritol 888 ATO& Precirol ATO 5) was melted in a porcelain dish over a water bath maintained at 75-80°C for 3 min and Nateglinide was gradually added with continuous stirring until uniformly mixed. The molten mixture was allowed to cool and solidify at room temperature crushed in a mortar and passed through a 40# sieve. The granules were compressed into flat–faced tablet using multi-station rotary tablet compression machine (Krishna engineering Pvt. Ltd. India) at a constant compression force.

Evaluation of drug - Excipient interaction*:* The pure drug, wax and the matrix tablet formulation were subjected to IR spectroscopy using FT-IR spectrophotometer. Their spectra were obtained over the wave number range of 4000 – 400 cm^{-1}.

In-vitro* drug release: In vitro* release studies were conducted using USP type II paddle apparatus (VDA-6D USP Std -VEEGO) run at 50 rpm. The buffer was kept at thermostatically controlled temperature of 37±0.5°C. The test was carried out in 900 ml of 0.01 M HCl for 2 h and then replaced with phosphate buffer (pH 6.8) as the dissolution medium for another 10 h. The pH change of medium was effected by adding 4.32g of sodium hydroxide and 6.08 g of potassium

 ISSN: 2250-1177 CODEN (USA): JDDTAO

dihydrogen phosphate dissolved in 5 ml water to the previous acidic medium (0.1 M HCl)(17). Five milliliters samples were withdrawn at the time intervals of 1, 2, 3, 4, 5, 6….12 and replaced with equal volume of fresh dissolution medium. The samples were filtered through 0.45 µm filter and analyzed for drug content at 218 nm by UV spectrophotometer.

Formulation:

Table 1: Identical formulation table for all batches

Polymer used	Precirol ATO 5			Compretol 888		
	25%	35%	45%	25%	35%	45%
Drug (NATEGLINIDE)	324	324	324	324	324	324
Polymer	162.5	227.5	292.5	162.5	227.5	292.5
Dicalcium phoshphate	144	79	14	144	79	14
Mg.Stearate	13	13	13	13	13	13
Aerosil 200	6.5	6.5	6.5	6.5	6.5	6.5
TOTAL	650mg	650mg	650mg	650mg	650mg	650mg

RESULTS

Interaction between drug and wax was checked by FT-IR Spectroscopy.

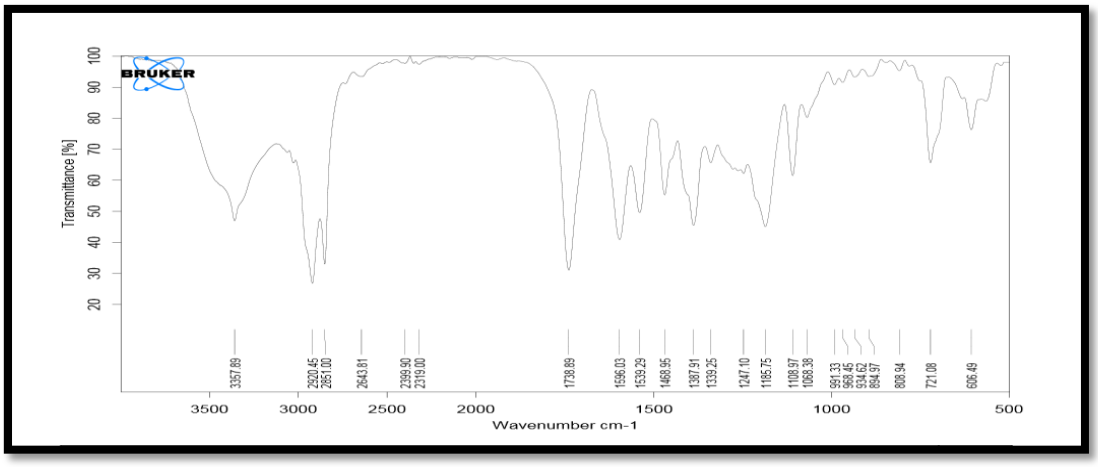

Figure 2: IR Spectrum of all excipients & Nateglinide

1. DIRECT COMPRESSION

Table 2: Pre-compression parameters of batch F1-F6 (Direct compression)

Formulation	Angle of Repose(°) (n=3) ±SD	Loose Bulk Density (g/cm3) ±SD	Tapped Bulk Density (g/cm3) ±SD	Hausners Ratio±SD	Carr's Index (%)±SD
F1	30.81±0.90	0.43±0.030	0.53±0.036	1.23±0.052	18.86±0.77
F2	29.75±0.81	0.44±0.034	0.56±0.028	1.27±0.060	21.40±0.25
F3	29.19±0.68	0.46±0.028	0.57±0.052	1.24±0.031	19.29±0.16
F4	28.40±0.74	0.47±0.019	0.58±0.043	1.23±0.047	18.98±0.29
F5	30.18±0.65	0.45±0.043	0.56±0.042	1.24±0.063	19.64±0.45
F6	32.39±1.02	0.46±0.035	0.57±0.051	1.23±0.058	19.29±0.87

Table 3: Post-compression parameters of batch F1-F6 (Direct compression)

Formulation	Hardness (Kg/Cm^2) ±SD	Friability (%)	Weight variation(mg) ±SD	Drug Content(%) ±SD	Swelling index (%)
F1	6.3±0.60	0.23	649±5.12	98.51±0.60	10.1
F2	6.5±0.28	0.21	650±4.94	99.12±0.42	25.6
F3	6.4±0.40	0.19	648±6.39	99.82±0.48	37.9
F4	6.5±0.71	0.17	650±5.38	99.54±0.71	24.4
F5	6.4±0.80	0.14	649±4.29	99.89±0.38	41.9
F6	6.4±0.58	0.13	649±4.35	99.64±0.66	54.6

Table 4: *In-Vitro* Drug Release data of F1 to F6

Time (h)	*In-Vitro* Drug Release at 37^0±0.5°C, 50 RPM					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
1	3.11	2.63	2.34	2.5	3.13	0.85
2	10.26	11.13	5.6	8.38	6.43	1.18
3	17.22	14.82	9.32	12.27	8.57	2.1
4	26.62	17.21	13.53	18.53	12.38	4.17
5	30.39	18.33	17.11	22.64	14.75	6.42
6	33.67	21.46	21.34	29.52	19.37	9.1
7	34.28	24.52	24.66	33.77	23.56	11.4
8	39.88	26.67	27.43	36.5	27.54	13.34
9	42.31	29.33	29.16	39.71	30.64	15.72
10	47.37	31.74	31.42	42.35	34.77	17.36
11	51.32	41.03	33.48	43.66	41.36	19.83
12	53.63	46.12	37.78	44.15	45.87	21.43

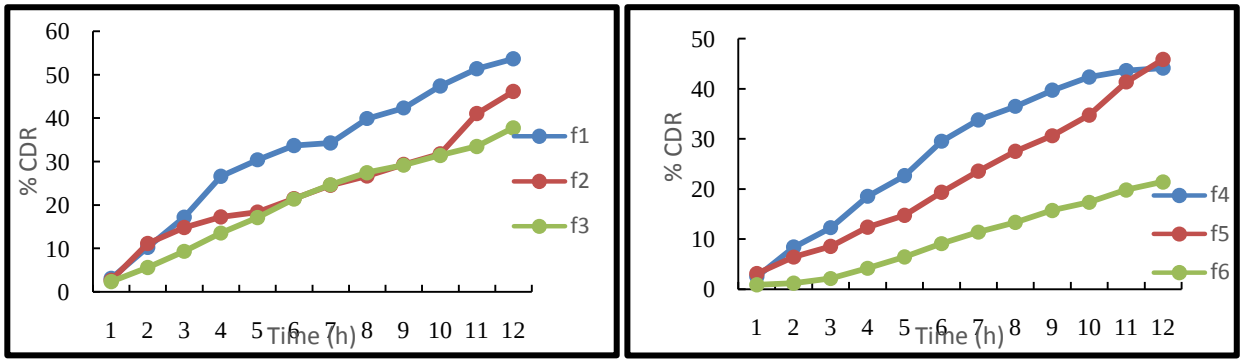

Figure 3: *In-VitroIn-Vitro* Drug Release of formulations F1 to F6

2. CO-PROCESSING

Table 5: Pre-compression parameters of batch F7-F12 (Co-processing)

Formulation	Angle of Repose(°) (n=3) ± S.D	Loose Bulk Density (g/cm3) ±S.D	Tapped Bulk Density (g/cm3) ±S.D	Hausners Ratio) ±S.D	Carr's Index (%)) ±S.D
F7	31.22±0.84	0.45±0.021	0.56±0.054	1.24±0.061	19.64±0.93
F8	33.04±0.32	0.46±0.037	0.55±0.044	1.19±0.052	16.35±0.61
F9	29.65±0.55	0.44±0.024	0.54±0.041	1.22±0.047	22.72±0.45
F10	27.25±0.74	0.47±0.029	0.56±0.063	1.20±0.084	16.18±0.77
F11	28.58±0.86	0.45±0.027	0.54±0.032	1.20±0.063	16.66±0.45
F12	31.20±0.40	0.46±0.035	0.57±0.061	1.23±0.038	19.29±0.57

Table 6: Post-compression parameters of batch F7-F12

Formulation	Hardness (Kg/Cm^2) ±SD	Friability (%)	Weight variation(mg) ±SD	Drug Content(%)±SD	Swelling index (%)
F7	6.7±0.27	0.14	650±4.08	99.85±0.12	12.3
F8	6.2±0.84	0.12	648±3.97	99.56±0.34	23.5
F9	6.4±0.79	0.10	649±6.41	98.17±0.87	39.6
F10	6.3±0.61	0.15	648±5.92	97.9±0.65	23.7
F11	6.6±0.85	0.15	649±7.81	99.74±0.14	43.6
F12	6.7±0.93	0.13	650±4.16	98.89±0.10	61.8

Table 7: *In-Vitro* Drug Release datas of F7 to F12

Time (h)	*In-Vitro* Drug Release at 37^0±0.5°C, 50 RPM					
	F7	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0
1	10.10	4.55	3.67	11.60	15.86	1.94
2	18.47	11.43	11.12	23.72	27.06	3.83
3	28.33	19.24	16.55	33.47	34.12	5.96
4	37.44	25.35	22.80	37.56	41.37	8.1
5	43.60	36.76	27.49	42.33	44.16	9.73
6	48.72	41.40	31.36	49.13	48.43	13.43
7	54.43	48.69	35.21	57.15	51.20	16.6
8	63.34	53.23	41.17	61.48	55.63	19.58
9	71.56	59.92	44.83	65.52	59.55	22.67
10	77.89	63.53	49.59	68.84	62.74	24.14
11	85.54	70.47	52.58	72.48	65.38	28.45
12	87.92	75.01	56.71	83.20	66.47	33.32

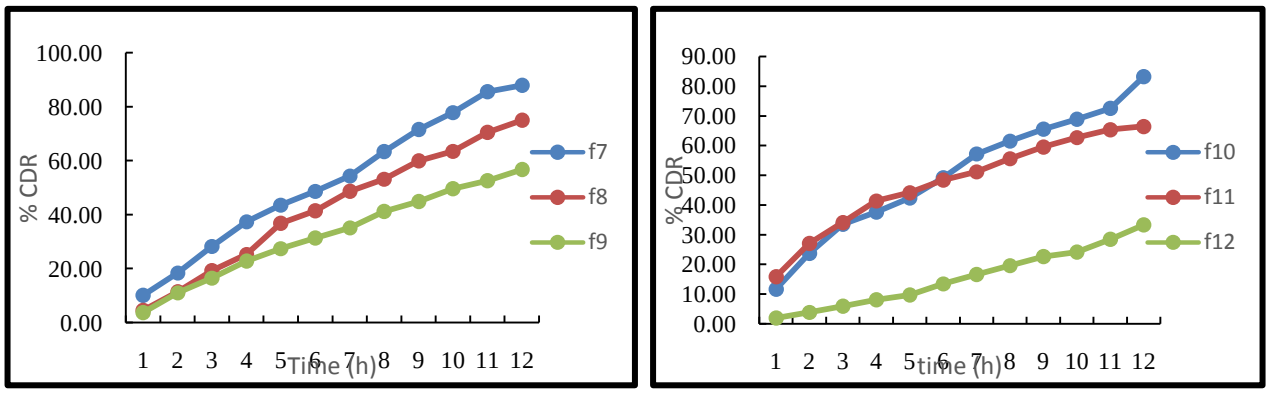

Fig 4: *In-VitroIn-Vitro* Drug Release of formulations F7 to F12

3. MELT GRANULATION

Table 8: Pre-compression parameters of batch F13-F18

Formulation	Angle of Repose(°) (n=3)	Loose Bulk Density (g/cm3)	Tapped Bulk Density (g/cm3)	Hausners Ratio	Carr's Index (%)
F13	18.20±0.88	0.59±0.030	0.66±0.045	1.12± 0.06	10.06±0.72
F14	19.87±0.43	0.67±0.028	0.72±0.032	1.07± 0.05	6.94±0.93
F15	17.07±1.01	0.58±0.034	0.64±0.037	1.10±0.07	9.37±0.60
F16	19.41±0.98	0.62±0.042	0.68±0.029	1.09±0.07	8.88±0.43
F17	19.43±0.79	0.57±0.011	0.62±0.050	1.08±0.09	8.09±0.38
F18	16.65±0.47	0.57±0.052	0.63±0.064	1.19±0.04	9.52±0.62

Table 9: Post-compression parameters of batch F13-F18

Formulation	Hardness (Kg/Cm^2) ±SD	Friability (%)	Weight variation(mg) ±SD	Drug Content(%) ±SD	Swelling index (%)
F13	6.5±0.38	0.13	650±4.65	99.89±0.50	22.9
F14	6.8±0.61	0.14	647±5.29	99.89±0.76	36.4
F15	6.3±0.29	0.13	648±3.39	99.89±0.47	42.3
F16	6.4±0.51	0.19	649±5.02	99.89±0.58	29.1
F17	6.6±0.27	0.14	648±4.92	99.64±0.60	34.9
F18	6.2±0.74	0.17	500±5.16	99.85±0.34	53.5

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Table 10: *In-Vitro* Drug Release datas of F13 to F18

Time (h)	*In-Vitro* Drug Release at 37^0±0.5°C, 50 RPM					
	F13	**F14**	**F15**	**F16**	**F17**	**F18**
0	0	0	0	0	0	0
1	11.47	11.06	8.43	9.12	10.21	7.42
2	24.42	19.65	14.96	11.36	16.80	11.15
3	40.62	33.04	23.25	20.82	24.15	17.14
4	48.99	38.47	28.74	36.74	28.68	20.96
5	58.79	46.07	33.62	43.06	34.49	25.41
6	67.13	53.34	38.39	50.61	41.06	28.94
7	72.47	60.62	43.53	62.21	47.44	32.12
8	79.05	66.07	48.68	76.15	51.88	36.06
9	84.05	70.84	52.42	83.90	59.34	39.15
10	90.36	75.05	56.43	89.97	64.89	42.88
11	92.13	82.61	62.12	91.25	66.21	48.25
12	94.55	86.54	68.32	92.10	71.45	54.13

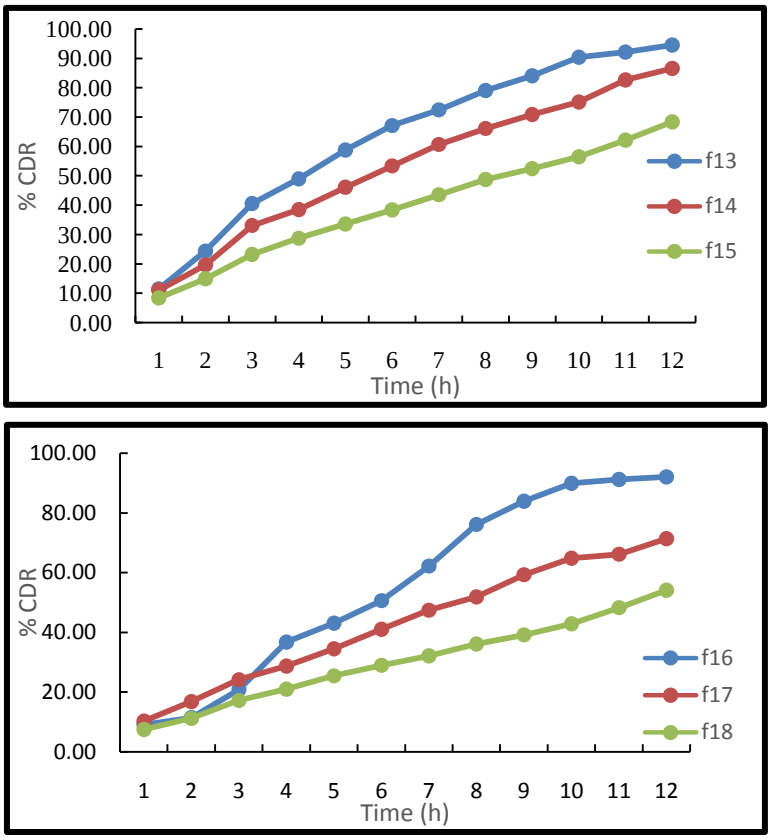

Fig 5: *In-VitroIn-Vitro* Drug Release of formulations F13 to F18

DISCUSSION:

The study showed that Precirol ATO 5 is an appropriate waxy matrix former for sustained release of low water-soluble drug such as Nateglinide.MG technique fits completely into the predetermined parameter and criteria whereas, other two techniques lack behind. Sustained release profiles can be achieved by any of three methods using Precirol ATO 5 at higher proportion but MG technique achieved 12 h release profile with lesser amount of was as compare to other methods. Formulation F13 was given 94.55% drug release in 12h which was optimizing batch.

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 ISSN: 2250-1177 CODEN (USA): JDDTAO