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FORMULATION AND INVITRO EVALUATION OF SUSTAINED RELEASE FORMULATION OF NATEGLINIDE

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INTRODUCTION

Now a day's conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics. Matrix system is the release system which prolongs and controls the release of the drug, which is dissolved or dispersed. A matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Sustained release system generally do no order type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat action tablet are an alternative method of sustained release in which multiple doses of drug are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval. Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before release, for example. Enteric coated tablet 3. A sustained release dosage form will provide a therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in a peak concentration ratio 4,5. Numerous drug delivery techniques have been developed to sustain the release of drugs, including triple-layered tablets (Geomatrix® t echnology) and osmotic pumps with laser drilled holes (OROS® t echnology). These technologies are intricate and relatively expensive to manufacture.

Advantages of sustained release dosage forms

1) The frequency of drug administration is reduced.
2) Patient compliance can be improved.
3) Drug administration can be made more convenient as well.
4) The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
5) Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
6) The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.

Disadvantages of sustained release dosage forms

1) Poor invitro and invivo correlations.
2) Probability of dose dumping.
3) Reduced potential for dose adjustment.
4) Cost of single unit higher than conventional dosage forms.
5) Increase potential for first pass metabolism.
6) Requirement for additional patient education for proper medication.
7) Decreased systemic availability in comparison to immediate release conventional dosage forms.

The general consensus is that controlled release denotes systems, which can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body. In other words, the systems attempts to control drug concentration in the target tissue or cells. Thus, prolonged release or sustained release systems, which only prolonged therapeutic blood or tissue levels of the drug for an extended period of time, cannot be considered as controlled release systems by this definition. They are distinguished from rate-controlled drug delivery systems, which are able to specify the release rate and duration in vivo precisely, on the basis of simple invitro tests. Drug targeting; on the other hand, can be considered as a form of controlled release in that exercises spatial control of drug release within the body. In general, controlled delivery attempts to:

- Sustain drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern.

- Localize drug action by spatial placement of a controlled release system (Usually rate-controlled) adjacent to or in the diseased tissue or organ.
- Target drug action by using carriers or chemical derivatization to deliver drug to a particular "target" cell type.

The term "sustained release" is known to have existed in the medical and pharmaceutical literature for many decades. It has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of therapeutic agent such that its appearance in the systemic circulation is delayed and/or prolonged and its plasma profile is sustained in duration.

The usual goal of an oral sustained-release product is to maintain therapeutic blood levels over an extended period. The duration of action significantly influences the design of oral SR delivery system and it is dependent on the biological half-life. Factors influencing the biological half-life of a drug include its elimination, metabolism and distribution patterns. Drugs with short half-lives required frequent dosing to minimize fluctuations in the blood levels. SR dosage forms would appear very desirable for such drugs. For a given steady state drug concentration, the zero-order rate of release of a drug from its dosage form is directly proportional to its rate of elimination. Thus drug with very short half-lives require faster rate of release, for a modest duration of time while dosage form requires large dosage. In general, drugs with half-lives shorter than 2 hrs are poor candidates for sustained-release preparations. Compounds with long half-lives, more than 8 hrs, are also generally not used in sustaining forms, since there effect is already sustained

Polymers Used in Matrix Tablet

Hydrogels

Polyhydroxyethylemethylacrylate(PHEMA), Crosslinked polyvinyl alcohol (PVA), Cross-linked polyvinyl pyrrolidone(PVP), Polyethylene-oxide(PEO), Polyacrylamide (PA).

Soluble polymers

Polyethyleneglycol (PEG), Polyvinyl alcohol(PVA), Polyvinylpyrrolidone (PVP), Hydroxypropylmethylcellulose (HPMC).

Biodegradable polymers

Polylactic acid (PLA), Polyglycolic acid (PGA), Polycaprolactone (PCL), Polyanhydrides, Polyorthoesters.

Non-biodegradable polymers

Polyethylene vinyl acetate (PVA), Polydimethylsiloxane(PDS), Polyetherurethane (PEU), Polyvinyl chloride (PVC), Cellulose acetate (CA), Ethyl cellulose (EC).

Mucoadhesive polymers

Polycarbophil, Sodium carboxy methyl cellulose, Polyacrylic acid, Tragacanth, Methyl cellulose, Xanthan gum, Guar gum, Karaya gum, Locust bean gum.

METHODOLOGY

Analytical method development

Determination of Wavelength

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From s econdary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). Th e working solution was taken for determining the wavelength.

Determination of Calibration Curve

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From s econdary stock solution required concentrations were prepared (shown in Table) and those concentrations absorbance were found out at required wavelength.

7.3. Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$

$\tan \theta$ = Angle of repose

h = Height of the cone,

r = Radius of the cone base

Table: Angle of Repose values (as per USP).

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

Bulk Density = M / V_o

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides drops per minute and this was repeated until difference between succeeding measurement is less than 2% and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap = M / V

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

Table: Carr's index value (as per USP).

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

7.4. Formulation development of Tablets

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table. The tablets were prepared as per the procedure given below and aim is to prolong the release of Nateglinide. Total weight of the tablet was considered as 300mg.

Procedure

1) Nateglinide and all other ingredients were individually passed through sieveno □ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table: Formulation composition for tablets.

INGREDIENTS(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
NATEGLINIDE	120	120	120	120	120	120	120	120	120
CARBOPOL 940	30	60	90	-	-	-	-	-	-
HYDROXY ETHYL CELLULOSE	-	-	-	30	60	90	-	-	-
POLY VINYL ALCOHOL	-	-	-	-	-	-	30	60	90
EUDRAGIT RS 100	12	12	12	12	12	12	12	12	12
TALC	3	3	3	3	3	3	3	3	3
Mg. STEARATE	3	3	3	3	3	3	3	3	3
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
TOTAL TABLET WEIGHT	300	300	300	300	300	300	300	300	300

RESULTS AND DISCUSSION

The present study was aimed to developing Controlled release tablets of Nateglinide using various polymers. All the formulations were evaluated for physicochemical properties and in vitro drug release studies.

Analytical Method

Graphs of Nateglinide were tak en in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 220 nm, 223 nm respect ively.

Table: Observatio ns for graph of Nateglinide in 0.1N HCL (220 nm).

concentration	absorbance
0	0
2	0.16
4	0.32
6	0.46
8	0.65
10	0.79

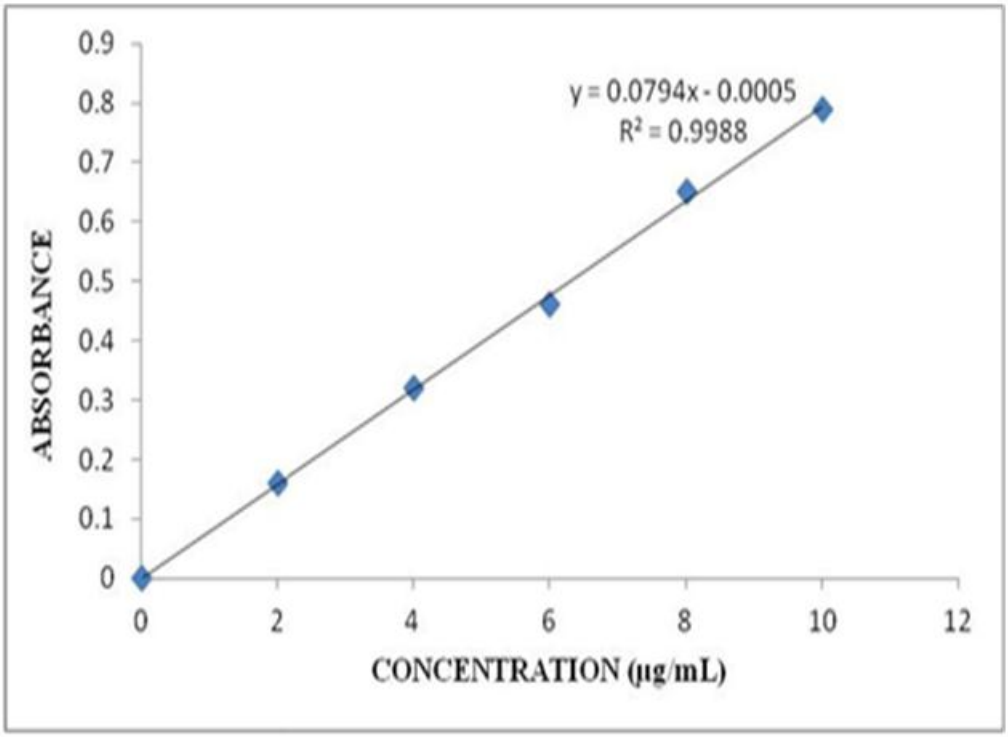
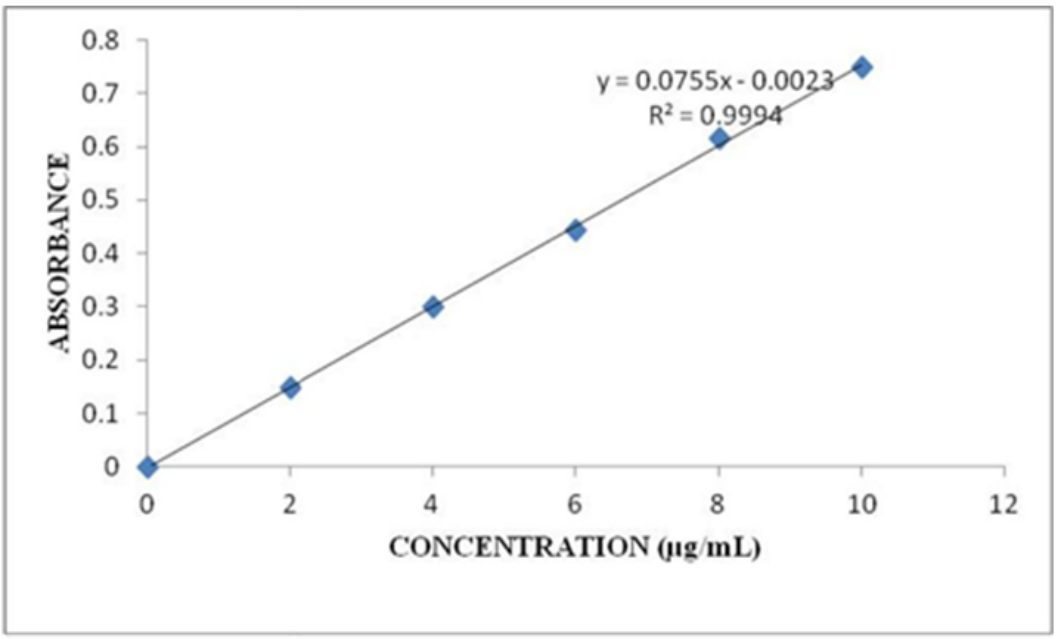


Figure: Sta ndard graph of Nateglinide in 0.1N HCL.

Observations for graph of Nateglinide in p H 6.8 phosphate buffer (2 23nm)

concentration	absorbance
0	0
2	0.148
4	0.298
6	0.442
8	0.614
10	0.748



EVALUATION

Characterisation of Precompression Blend

The precompression blend for Controlled tablets were characterized with respect to angle of repose, bulk density, tapped density, Hausner's ratio, Carr's index and drug content/ Assay shown in the Table. Angle of repose was less than 30° and Carr's index values were less than 18 for the precompression blend of all the batches indicating good to fair flowability and compressibility, Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Table: Physical Properties of Precompression Blend.

Formulation Code	Angle of repose (θ)	Bulk density (g/mL)	Tapped density(g/mL)	Carr's index (%)	Hausner's ratio
F1	26.76	0.526	0.612	14.0	1.16
F2	27.54	0.662	0.763	13.23	1.15
F3	24.65	0.695	0.823	15.5	1.18
F4	22.9	0.672	0.742	12.2	1.21
F5	28.3	0.643	0.624	14.2	1.11
F6	24.84	0.654	0.755	13.12	1.12
F7	28.68	0.782	0.869	11.0	1.11
F8	24.68	0.560	0.631	11.25	1.12
F9	25.16	0.628	0.714	14.27	1.17

Quality Control Parameters For tablets

Tablet quality control tests such as Average weight, hardness, and friability, thickness, and drug release studies in different media were performed on the compressed tablet.

Table: *In Vitro* quality control parameters for tablets.

Formulation codes	Average Weight (mg)	Hardness(kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	299.6	4.5	0.52	4.15	99.2
F2	300	4.4	0.68	4.46	98.6
F3	299.9	4.5	0.59	4.38	100.34
F4	299.5	4.4	0.68	424	99.98
F5	300.2	4.4	0.53	4.32	101.25
F6	298.7	4.4	0.59	4.56	99.30
F7	299.6	4.5	0.73	4.34	99.74
F8	294.7	4.4	0.64	4.45	97.54
F9	302	4.5	0.59	4.41	99.61

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

In Vitro Drug Release Studies

Dissolution Data of Nateglinide Tablets Prepared With Different Polymers.

TIME (hr)	% Cumulative Drug Release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
In dissolution media 0.1 N HCL									
0	0	0	0	0	0	0	0	0	0
0.5	4.59	3.96	3.296	4.90	3.66	2.88	4.710	3.544	2.936
1	9.15	7.10	6.71	11.94	8.14	7.13	8.370	6.776	5.074
2	17.97	11.61	7.89	15.32	12.14	12.89	13.27	10.733	8.326
In dissolution media 6.8 Phosphate Buffer									
3	19.07	13.46	12.18	18.36	15.45	18.46	17.80	12.193	11.275
4	36.18	25.81	18.81	35.23	29.15	34.44	31.35	20.82	19.85
5	41.16	32.43	27.50	52.71	49.98	44.05	45.43	37.02	34.10
6	52.88	41.22	38.47	70.74	69.94	52.90	58.90	45.62	45.77
7	73.36	58.09	52.22	86.74	77.58	74.41	65.91	57.11	54.61
8	84.04	66.27	63.35	99.10	81.95	79.15	74.44	69.14	68.06
9	90.91	77.12	75.30		88.70	92.61	83.30	77.61	73.04
10	99.68	89.98	84.01		99.74	98.98	94.52	87.91	81.25
11		98.87	89.07				98.63	90.25	86.67
12			93.54					97.52	91.25

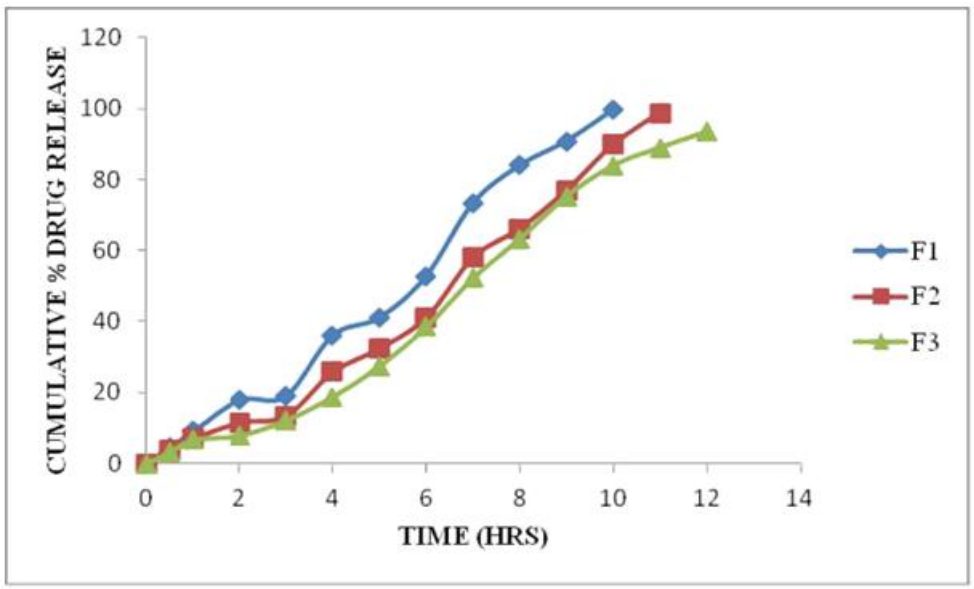


Fig: Dissolution data of Nate glinide Controlled release tablets containing Carbopol 940.

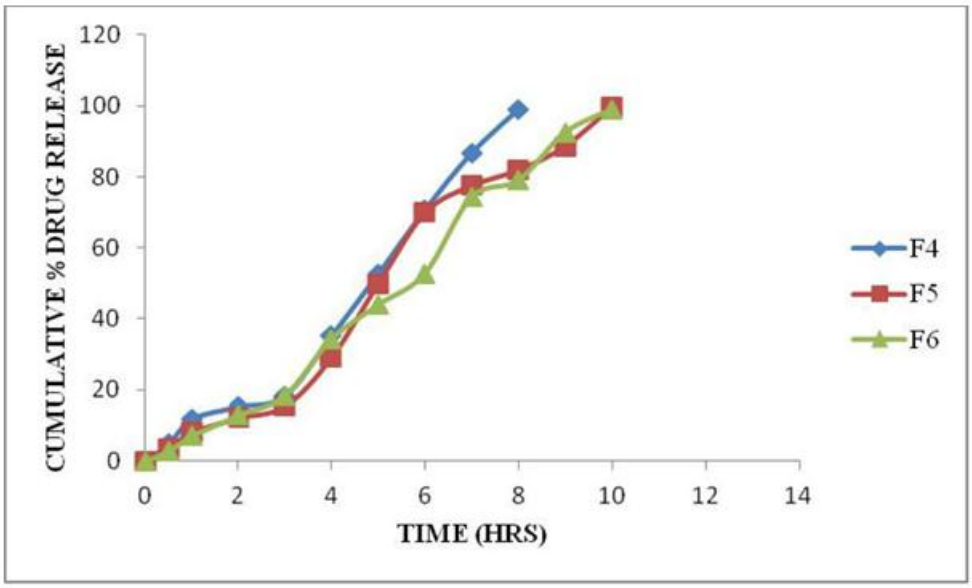


Fig: Dissolution data of Nate glinide Controlled release tablets containing Hydroxy Ethyl Cellulose.

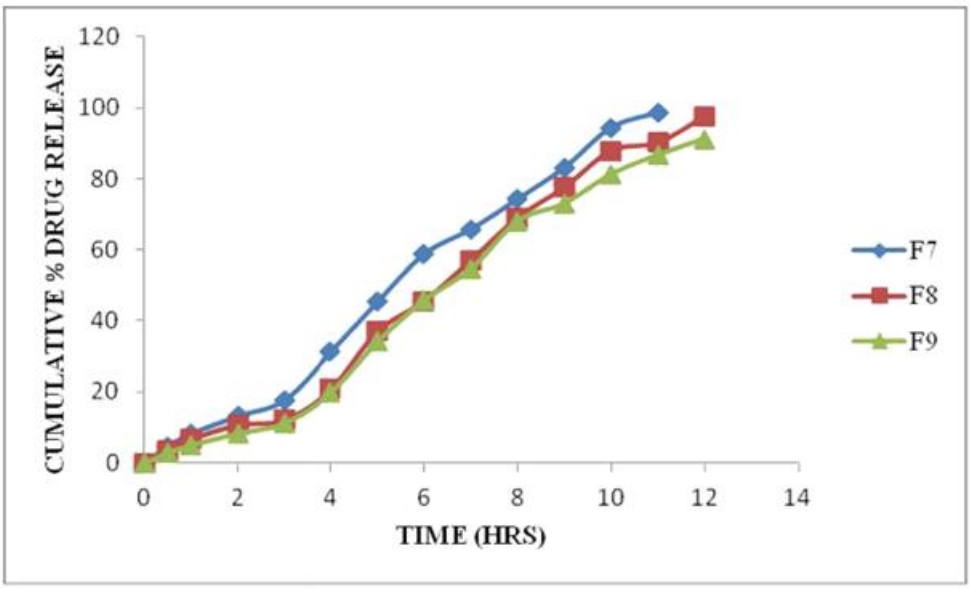


Fig: Dissolution data of Nateglinide Controlled release tablets containing Poly Vinyl Alcohol.

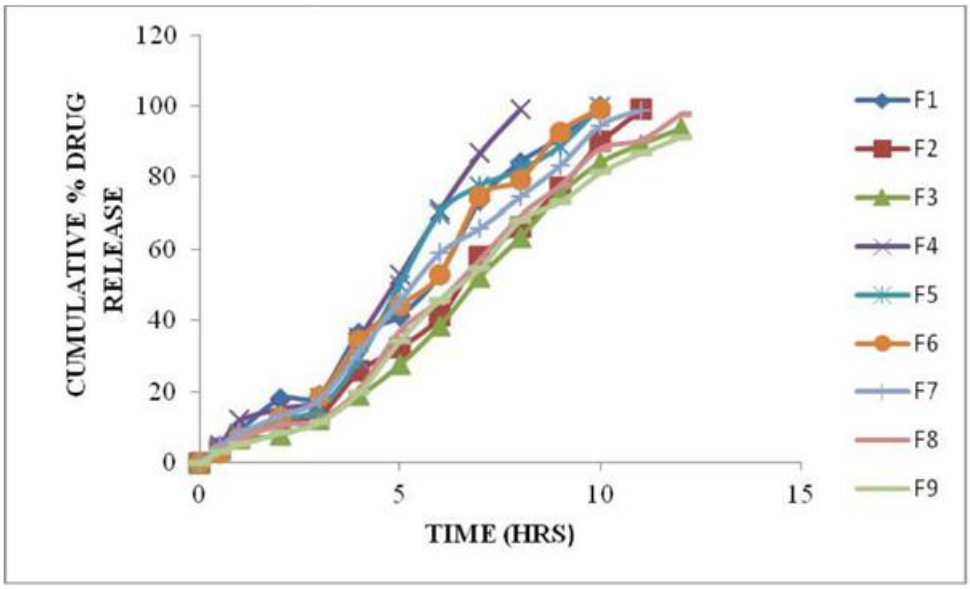


Fig: Dissolution data of Nateglinide Controlled release tablets All Formulations (F1-F9).

From the dissolution data it was evident that the formulations prepar ed with Hydroxy Ethyl Cellulose as polymer was unable to retard the drug release up to desired ti me period i.e., 12 hours.

Whereas the formulation s prepared with Carbopol 940 retarded the drug release in the concentration of 90 mg (F3 Formulation) retarded the drug release (93.5 4%) up to 12 hours(Required Time). Whereas the formulations prepared with Poly Vinyl Alcohol (F8 Formuylation) showed maximum of 97.52% in 12 hours with good retardation. Hence it was considered as optimised formulation (F8).

Application of Release Rate Kinetics to Dissolution Data for optimised formulation

Table no: Application kinetics for optimised formulation.

CUMULATIVE (%) RELEASEQ	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RATE (CUMULATIVE % RELEASE /t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
3.544	0.5	0.707	0.549	-0.301	1.984	7.088	0.2822	-1.451	96.456	4.642	4.586	0.055
6.776	1	1.000	0.831	0.000	1.970	6.776	0.1476	-1.169	93.224	4.642	4.534	0.107
10.733	2	1.414	1.031	0.301	1.951	5.367	0.0932	-0.969	89.267	4.642	4.469	0.172
12.193	3	1.732	1.086	0.477	1.944	4.064	0.0820	-0.914	87.807	4.642	4.445	0.197
20.82	4	2.000	1.318	0.602	1.899	5.205	0.0480	-0.682	79.18	4.642	4.294	0.347
37.02	5	2.236	1.568	0.699	1.799	7.404	0.0270	-0.432	62.98	4.642	3.979	0.663
45.62	6	2.449	1.659	0.778	1.735	7.603	0.0219	-0.341	54.38	4.642	3.789	0.853
57.11	7	2.646	1.757	0.845	1.632	8.159	0.0175	-0.243	42.89	4.642	3.500	1.141
69.14	8	2.828	1.840	0.903	1.489	8.643	0.0145	-0.160	30.86	4.642	3.137	1.505
77.61	9	3.000	1.890	0.954	1.350	8.623	0.0129	-0.110	22.39	4.642	4.445	1.823
87.91	10	3.162	1.944	1.000	1.082	8.791	0.0114	-0.056	12.09	4.642	2.818	2.346
90.25	11	3.317	1.955	1.041	0.989	8.205	0.0111	-0.045	9.75	4.642	2.295	2.505
97.52	12	3.464	1.989	1.079	0.394	8.127	0.0103	-0.011	2.48	4.642	2.136	3.288

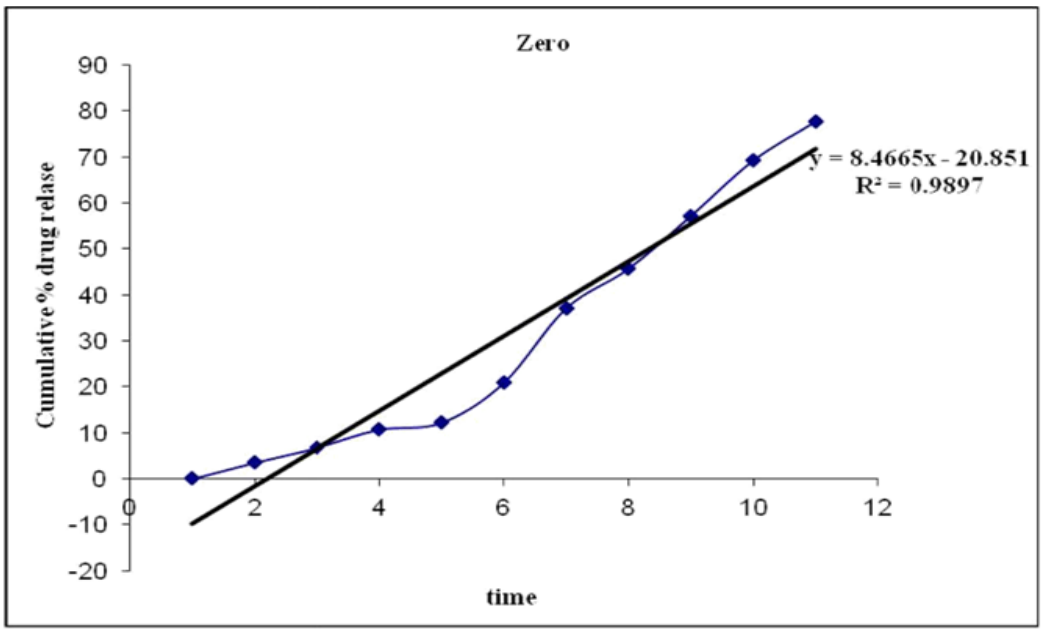


Fig: Zero order release kinetics.

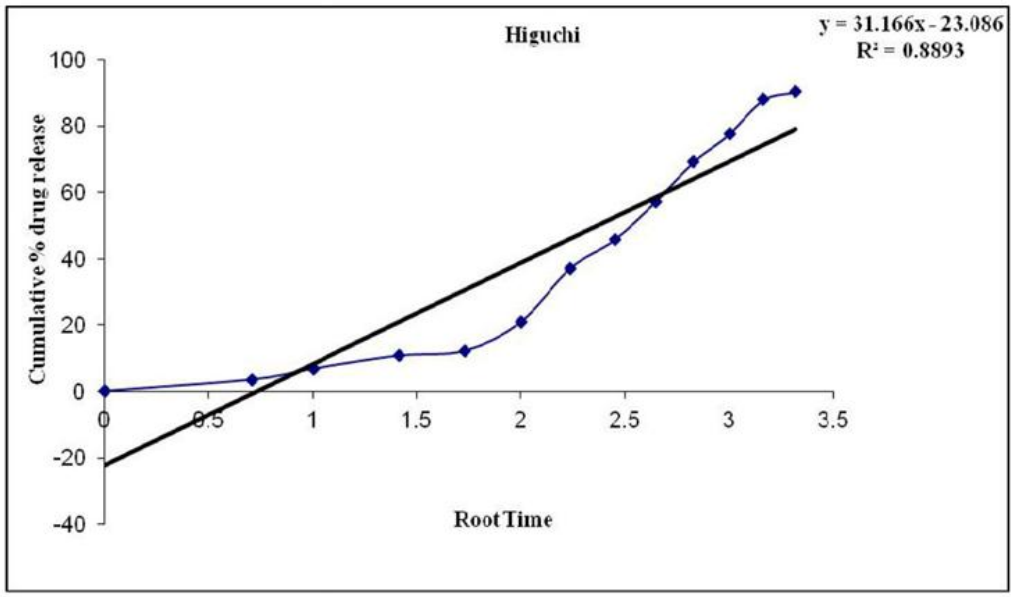


Fig: Higuchi release kinetics.

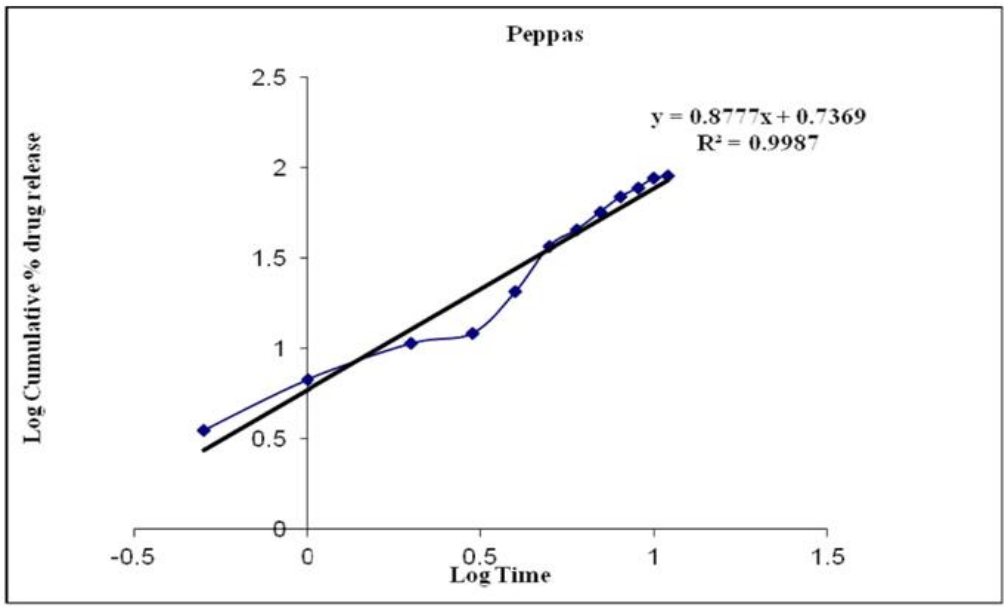


Fig: Kors mayer peppas release kinetics.

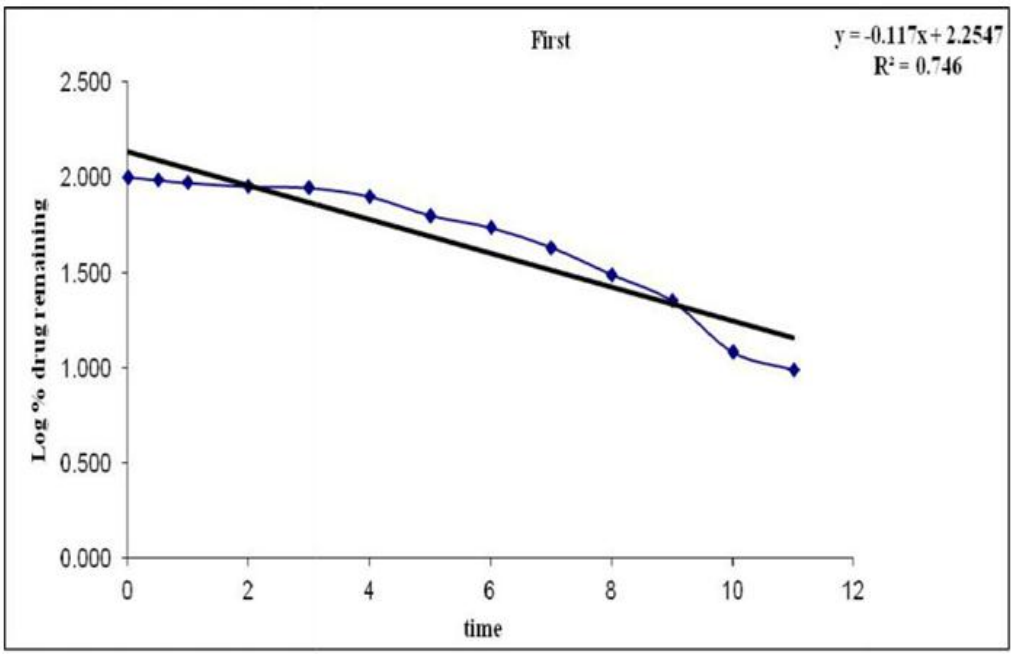


Fig : First order release kinetics.

Optimised formulation F8 was kept for release kinetic studies. From the above graphs it was evident that the formulation F8 was followed Peppas release mechanism.

CONCLUSION

The present investigation was carried out for controlling the Nateglinide drug release up to 12 hrs. For controlling the drug release polymers used such as Carbopol 940, Hydroxy Ethyl Cellulose, Poly Vinyl Alcohol.

From the investigation studies were found following:

- ✓ Standard graph was given that regression analysis R^2 value was 0.998, 0.999 in both 0.1 N HCL and pH 6.8 phosphate buffer.
- ✓ FTIR results were shown good compatibility between drug and excipients.
- ✓ All the pre and post compression studies such as Bulk density, Tapped density, Angle of repose, Carr's index, Hausners ratio, Weight variation, Thickness, Hardness, Drug content were found to be within limits.
- ✓ *In vitro* drug release studies revealed that among all formulations F8 formulation was considered as optimised formulation which contain Poly Vinyl Alcohol as polymer in the concentration of 60 mg.

Drug release kinetic studies were done for optimised formulation. It was followed Peppas release kinetics.

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