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Formulation development and *invitro* evaluation of pulsatile drug delivery system of Nebivolol Hydrochloride

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ABSTRACT

The aim of the present work was to develop a pulsatile drug release system of Nebivolol hydrochloride by using ethyl cellulose, xanthan gum, Hydroxy propyl methyl cellulose K15 M for the effective treatment of hypertension. This system is designed to mimic the circadian rhythm of the disease by releasing the drug after a predetermined lag time of 6 hrs. This Time controlled delivery system is capable of delivering drug when and where it is required most. All the formulations were prepared by direct compression method each consisting of a core and a coat ('core in cup' method). The core tablet containing the active ingredient was then coated with polymers such as Xanthan gum, Hydroxy propyl methyl cellulose K15 M and Ethyl cellulose in different proportions. These pulsatile tablets were subjected to various evaluation studies for the drug content, thickness and in-vitro release profile. The in vitro dissolution study of the prepared tablets was conducted initially for 2 hrs in simulated gastric fluid and after that medium was changed to intestinal fluid pH 7.4 for remaining 10 hrs. Among all the formulations F10 formulation showed maximum of 99% drug release, at the end of 12 hrs. It followed zero order and peppas release kinetics and thus matches with chrono-biological requirement of the disease.

Keywords - Chronotherapeutics, Circadian rhythm, Ethyl cellulose, Hydroxy propyl methyl cellulose K15 M, Pulsatile drug delivery, Time controlled drug delivery, Xanthum gum.

INTRODUCTION

Pulsatile Drug Delivery System

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery system for the most obvious advantage of the oral routes of the administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as the nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of the drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release. The principal rationale for the use of pulsatile release is for the drugs were a constant drug release, i.e., a zero-order release is not desired. The release of the drug as a pulse after a lag time (an interval of no drug release) has to be designed in such a way that a complete and rapid drug release follows the lag time.

In chronopharmacotherapy (timed drug therapy) drug administration is synchronizedwith biological rhythms to produce a maximal therapeutic effect and minimum harm to thepatient. By basing drug delivery on circadian patterns of Diseases, drug effect can be optimized and side effects can be reduced. If symptoms occur at daytime a conventional dosage form can be administered just prior the symptoms are worsening. If symptoms of a disease became worse during the night or in the early morning the timing of drug administration and the nature of the drugdelivery system need careful consideration. Pulsatile release is also useful for the targeting of the drug irritating the stomach or degradable therein, as well for drugs developing biological tolerance or with an extensive first-pass metabolism. This novel system is a so-called "core in cup". This novel system or a technique consists of three components which are core tablet, impermeable layer at the bottom and surrounding the tablet and hydrophilic swellable material on the top to produce brust release after predetermined lag time.

Physiochemical data of nebivolol hydro - chloride

Nebivolol is a highly cardio selective vasodilatory beta1 receptor blocker used in treatment of hypertension. It lowers blood pressure (BP) by reducing peripheral vascular resistance, and significantly increases stroke volume with preservation of cardiac output. The net hemodynamic effect of nebivolol is the result of a balance between the depressant effects of beta-blockade and an action that maintains cardiac output.

MATERIALS & METHODS

Table: 1 Ingredients and source

List of equipments

Sl.no	Ingredients	Source
1	Nebivolol	Gift Sample from Dr. Reddy's Labs.
2	Hydroxyl propyl methyl cellulose $K_{15}M$	SD fine chemicals, Mumbai
3	Carbopol	SD fine chemicals, Mumbai
4	Avicel ph102(mcc)	SD fine chemicals, Mumbai
5	Cross povidone	SD fine chemicals, Mumbai
6	Magnesium stearate	SD fine chemicals, Mumbai
7	Xanthum gum	SD fine chemicals, Mumbai
8	Ethyl cellulose	SD fine chemicals, Mumbai
9	Aerosil	SD fine chemicals, Mumbai
10	Talc	SD fine chemicals, Mumbai

Table 2: Equipments

S.No.	Name of the Equipment	Model
1.	Electronic weighing balance	Scale-Tec
2.	Friabilator	Roche Friabilator Electrolab, Mumbai
3.	Laboratory oven	Dtc-00r
4.	Compression machine	Cmd (Cadmach)
6.	Tablet hardness tester	Pfizer Hardness Tester, Mumbai
7.	UV	Labindia Uv 3000+
8.	Dissolution apparatus	Electrolab TDT-08L
9.	Vernier calipers	Cd-6"Cs

METHODOLOGY

Analytical Method Development

Preparation of Standard Calibration Curve for nebivolol hydrochloride

Reagents

0.1N hydrochloric acid Buffer Solution
6.8 pH Buffer Solution

Method of preparation of 0.1n Hcl and 6.8 buffer solutions

Preparation of 0.1 N Hcl Solutions

0.1N Hcl was prepared by diluting 8.5 ml of concentrated Hydrochloric acid to 1000 ml distilled water.

Preparation of 6.8 pH phosphate buffer solution

27.22g of monobasic potassium phosphate was weighed and diluted up to 1000 ml to get stock solution of monobasic potassium phosphate. 8g Sodium hydroxide was weighed and diluted up to 1000ml to get 0.2M sodium hydroxide solution. 50 ml of the monobasic potassium phosphate solution was taken from the stock solution in a 200-mL volumetric flask and 22.4 ml of sodium hydroxide solution from stock solution of 0.2M sodium hydroxide solution was added and then water was used to make up the volume.

Principle

Standard solution of nebivolol hydrochloride by using 0.1 N Hcl

100mg of the drug is dissolved in 100ml of methanol. This is the first stock solution.10ml of 1st stock solution is diluted with 100ml of 0.1N Hydrochloric acid buffer. This is 2nd stock solution. Now from 2nd stock, various concentrations of 2ug/ml, 4ug/ml, 6ug/ml, 8ug/ml, and 10ug/ml were prepared by using same 0.1 N Hydrochloric acid buffers. Blank was also prepared with the same buffer composition except the drug. All the samples were analyzed at 276 lambda max with respect to the blank.

Standard solution of Nebivolol Hydrochloride by using 6.8 Buffer Solution

100mg of the drug is dissolved in 100ml of methanol. This is the first stock solution. 10ml of 1st stock solution is diluted with 100ml of 6.8 buffers. This is 2nd stock solution. Now from 2nd stock, various concentrations of 10ug/ml, 20ug/ml, 30ug/ml, 40ug/ml, and 50ug/mlwere prepared by using same 6.8 buffers. Blank was also prepared with the same buffer composition except the drug. All the samples were analyzed at 276 lambda max with respect to the blank.

Formulation of Nebivolol ER Tablets by Direct Compression Method

Preparation of ER Tablets

All the excipients except Mg stearate were cosifted through # 40 seive & blended in a poly bag for 10 min. To the above mixture magnesium stearate was added & lubricated by blending in a poly bag for 5 min. ER tablets of 250 mg weight were prepared by direct compression method using 7 mm concave punch with single station tablet compression machine.

Table 3: Formulations Polymer (cup) layer over the Nebivolol hydrochloride tablet

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
HPMC K15M	50	65	75	100	-	-	-	-	-	-	-	-
Xanthan Gum	-	-	-	-	50	65	75	100	-	-	-	-
Ethylcellulose	-	-	-	-	-	-	-	-	50	65	75	100
Avicel	198	183	173	148	198	183	173	148	198	183	173	148
Mg. Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	250	250	250	250	250	250	250	250	250	250	250	250

Table 4: Formulation of Nebivolol Hydrochloride Tablet (Core Tablet)

Ingredients	Weight in mg
Nebivolol	10
Avicel	61
Crosspovidone	7
Pvpk30	20
Talc	1
Aerosil	1
Total weight	100

Method

The tablets will be prepared by using Karnavati Mini press with suitable flat faces punches. The system will consist of a core- in-cup tablet. The core tablet consisting of Nebivolol will be made by flat punches 8 mm. An impermeable coating cup consisting of cellulose acetate propionate will be applied at the bottom and core tablet is placed at the centre further the cellulose acetate propionate is placed at the sides of the tablet except the top. On the top hydrophilic swellable material will be placed and total material will be compressed to produce core in cup system.

Evaluation of tablets

The formulated tablets were evaluated for the following Pre, post compression quality control studies & In vitro Buoyancy studies and dissolution studies.

Pre Compression studies include

Angle of Repose., Density:Bulk density (BD), Tapped density (TD)., Carr's Index and Hausner's Ratio.

Post compression studies include

General appearance, Average weight/Weight Variation, Thickness, Hardness test, Friability test and Invitro

Dissolution Study.

RESULTS AND DICUSSION

Construction of Standard calibration curve of Nebivolol hydrochloride in 0.1N HCl

The absorbance of the solution was measured at 282nm, using UV spectrometer with 0.1N HCl as blank. The values are shown in table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml.

Table 5: Standard Calibration graph values of Nebivolol hydrochloridein 0.1N Hcl

Concentration (µg/ml)	Absorbance
0	0
10	0.112
20	0.208
30	0.315
40	0.42
50	0.519

Standard plot ofnebivolol HCl plotted by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown graph

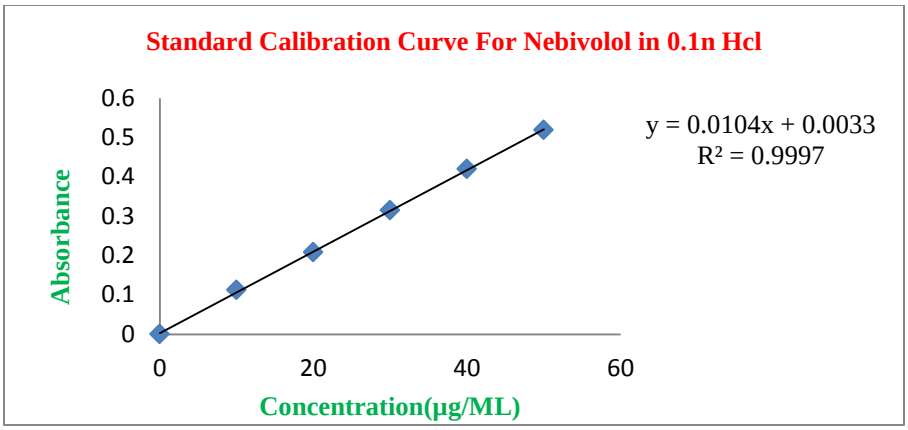

Figure 1: Standard calibration curve of Nebivolol hydrochloride in 0.1N Hcl at λ_{Max} = 282nm

Inference

The standard calibration curve of Nebivolol hydrochloride in 0.1N HCl showed good correlation with regression value of 0.999

Construction of Standard calibration curve of Nebivolol Hyrocloride in 6.8 phosphate buffer

The absorbance of the solution was measured at 282nm, using a UV spectrometer with 6.8 phosphate buffer as blank. The values are shown in table no 20. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 10 to 50 µg/ml

Table 6: Standard Calibration graph values of Nebivolol Hydrochloride in 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance (λ_{Max} = 282nm)
0	0
10	0.105
20	0.199
30	0.31
40	0.42
50	0.508

Standard plot ofNebivolol hydrochlorideplotted by taking the absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown graph

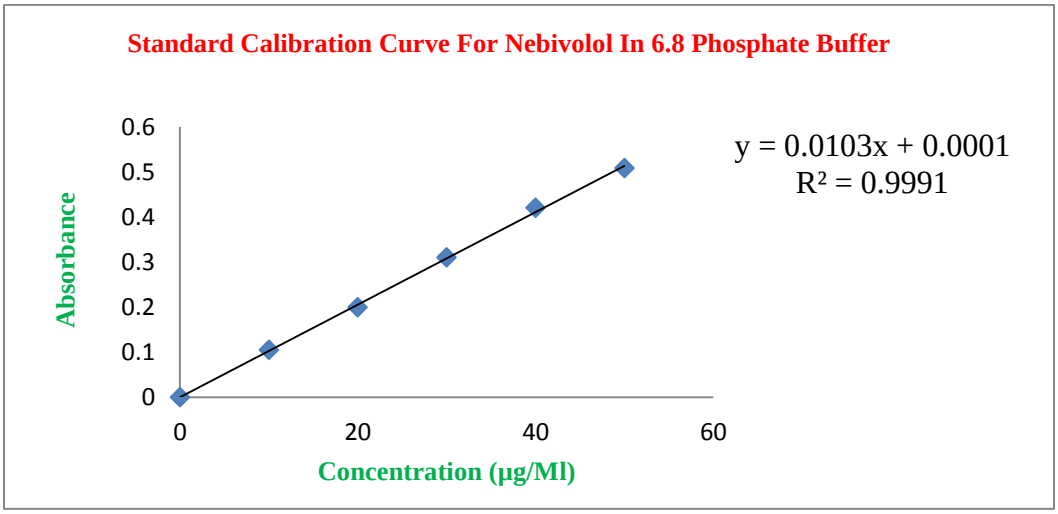

Figure 2: Standard calibration curve of Nebivolol hydrochloride in 6.8 phosphate buffer

Inference

The standard calibration curve of Nibevolol hydrochloride in 6.8 phosphate buffer showed good correlation with the regression value of 0.999

Drug-Excipients Compatibility Studies by FTIR –Studies

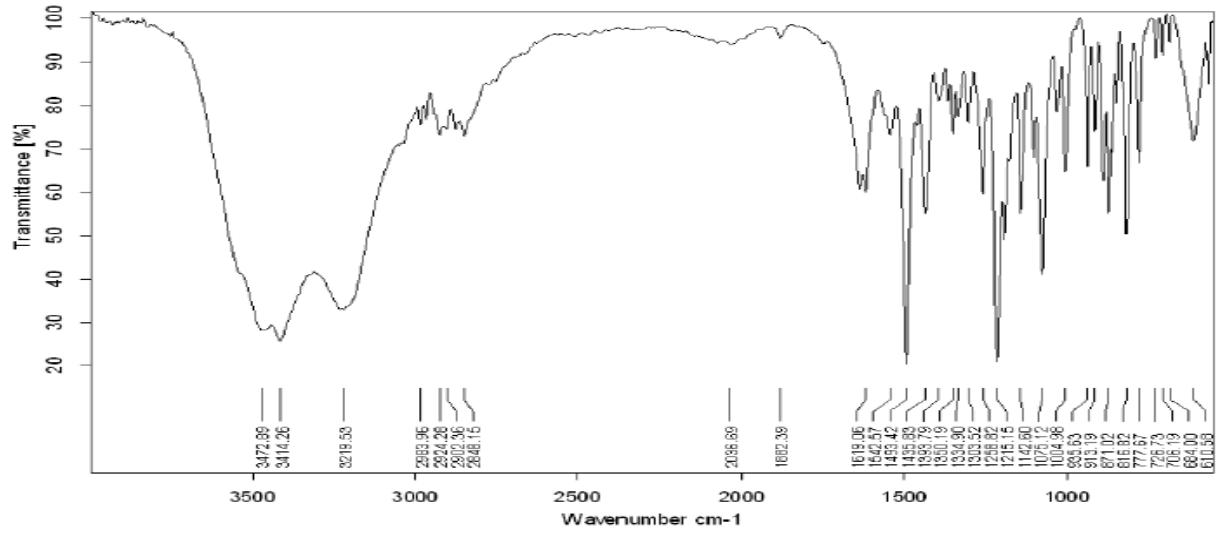

Figure 3: FTIR - of pure API – NebivololHCl

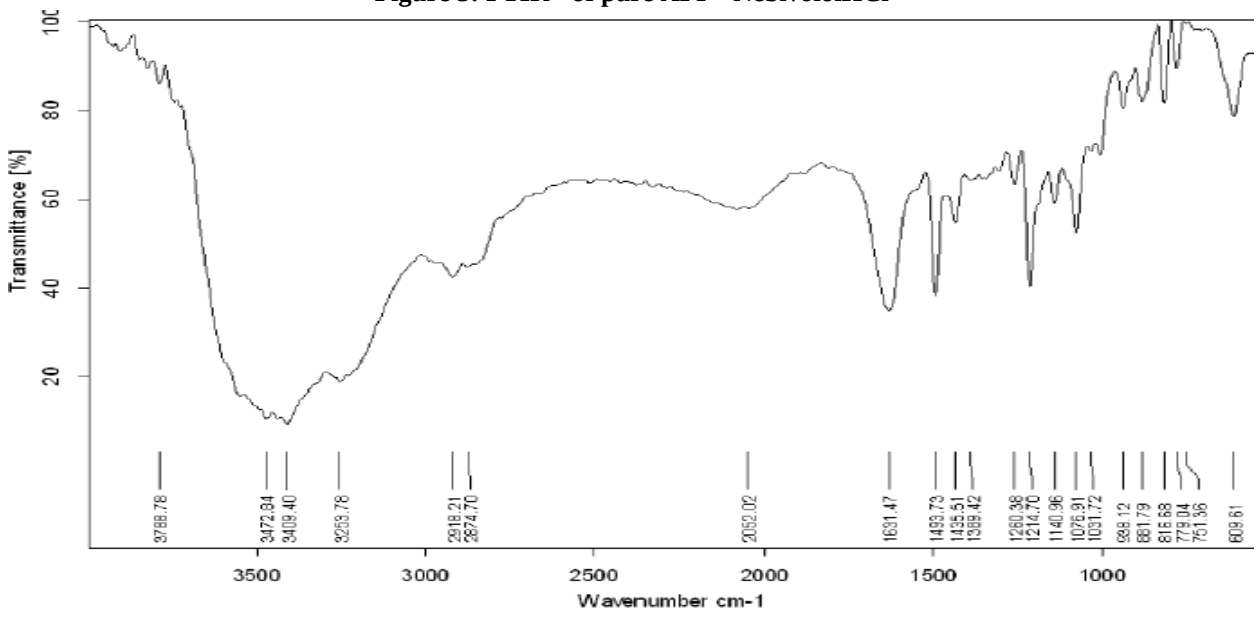

Figure 4: FTIR - of pureNebivololHCl+ALL Excipients

In Vitro Dissolution Study

900 ml of 0.1N HCl was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of $37^0C \pm 0.5^0C$. A tablet was placed in each vessel and was covered; the apparatus was operated up to 2 hrs at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Now immediately after the 2nd hour, 900 ml of 6.8 phosphate buffer solutions should be replaced in place of 0.1 N HCl solutions in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of $37^0C \pm 0.5^0C$. Again the tablets should be placed in each vessel and was covered; the apparatus was operated up to 10 hrs at 50 rpm. At

definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} =282 nm using a UV-spectrophotometer.

Table 7: *Invitro* Dissolution Studies for Nebivolol Hydrochloride ER Table

TIME (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.01N HCL												
0	0	0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	18	12	8	5	0	0	0	0
2	8	6	4	2	31	28	21	15	10	0	0	0
6.8 pH Phosphate buffer												
4	12.8	10.8	9	7	43	35	30	19.74	23	11	0	0
6	25.9	20.9	16.45	13.12	55	48	45	27.96	49	21	15	13
8	48.6	35.8	31.8	25.26	76	67	64	37.83	68	50	21	20
10	63.4	49.6	44.6	41.23	98	89	83	51.83	89	78	48	50
12	85.6	71.4	65.9	63.78	100	100	97	65.86	100	99	61	63

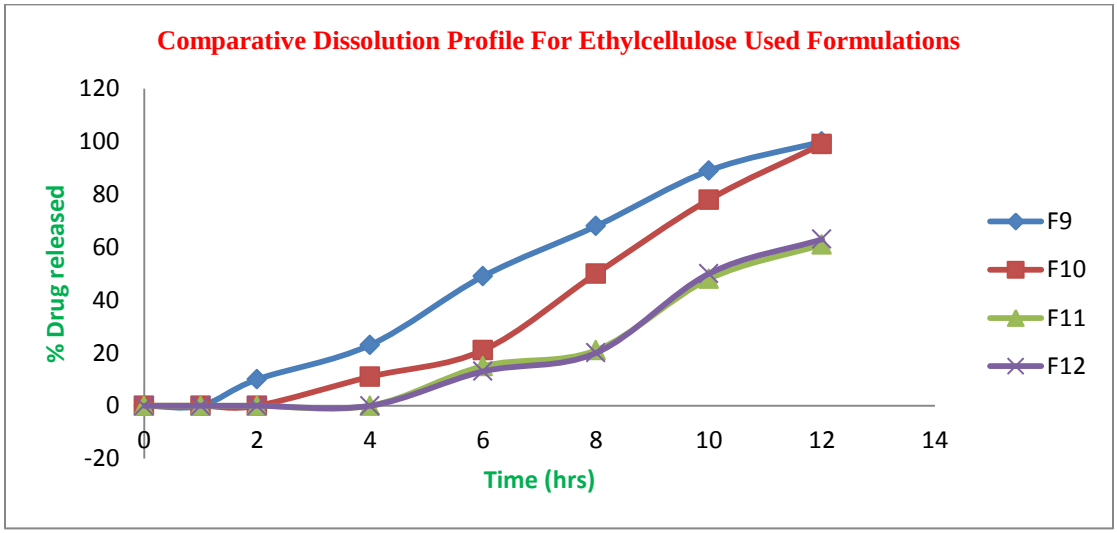

Figure 5: Comparative dissolution profile for F9, F10, F11 and F12 ER Tablets

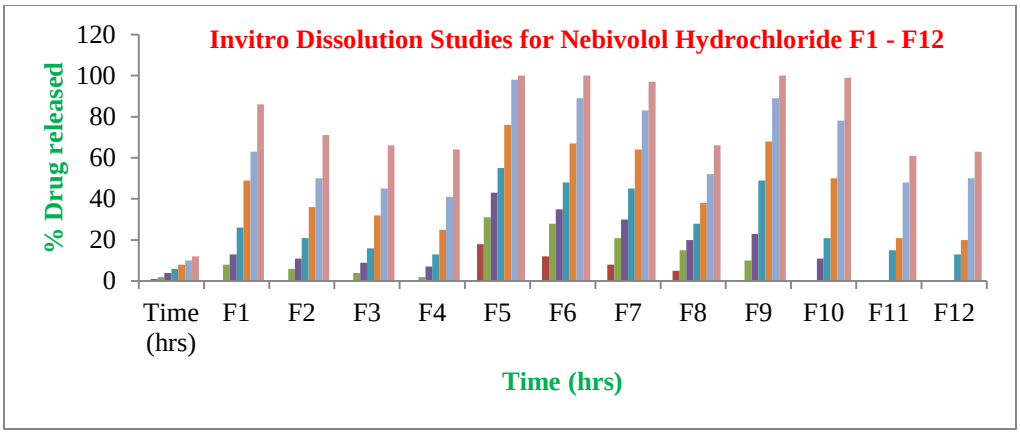

Figure 6: *Invitro* dissolution studies for nebivolol HCl F1 – F12

Table 8: Drug release kinetics

Formulation Code	Zero order		First order		Higuchi		Peppas	
	R^2 Value	K Value	R^2 Value	K Value	R^2 Value	K Value	R^2 Value	N Value
F1	0.962	7.167	0.840	0.026	0.805	24.34	0.966	1.670
F2	0.952	5.784	0.863	0.017	0.790	19.55	0.979	1.606
F3	0.937	5.309	0.859	0.014	0.764	17.79	0.992	1.623
F4	0.903	5.014	0.819	0.013	0.714	16.56	0.984	1.692
F5	0.975	8.269	0.845	0.070	0.955	30.37	0.984	0.692
F6	0.986	8.103	0.773	0.058	0.928	29.18	0.972	0.805
F7	0.994	8.033	0.816	0.046	0.913	28.57	0.984	0.96
F8	0.983	5.177	0.937	0.015	0.893	18.31	0.968	0.945
F9	0.988	9.097	0.790	0.060	0.876	31.79	0.953	1.767
F10	0.928	8.559	0.654	0.055	0.743	28.43	0.949	2.081
F11	0.876	5.158	0.827	0.013	0.677	16.82	0.802	1.870
F12	0.859	5.297	0.807	0.014	0.656	17.18	0.802	1.870

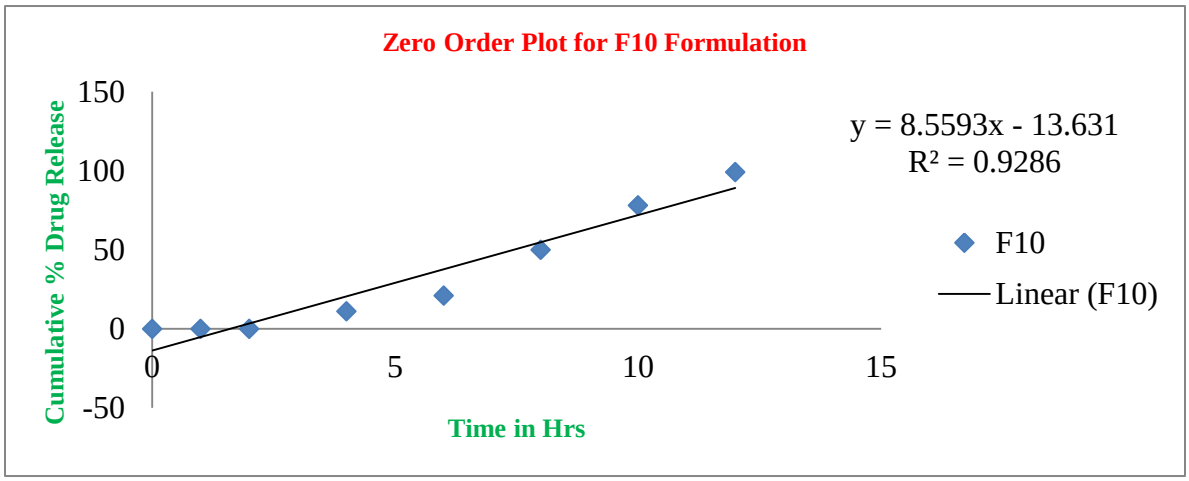

Figure 7: Zero order plot for best formulation F10 for ER Tablets

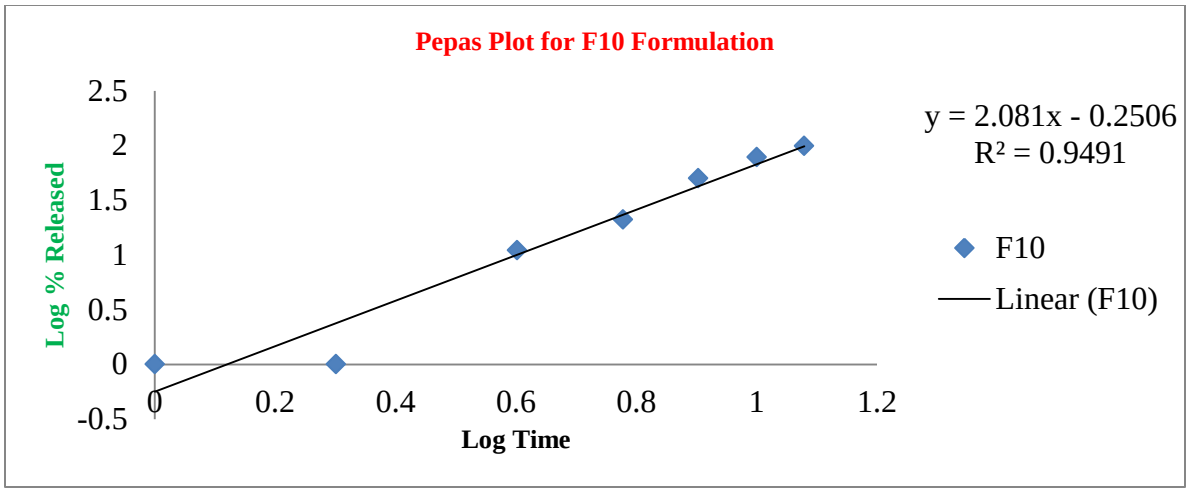

Figure 8: Kors Mayers Pepas plot for best formulation F10 for ER tablets

Inference

- Among the different control release polymers Ethyl cellulose was showing highest drug release retarding capacity.
- F10 formulation at drug:polymer at 1:10 was showing the satisfactory results by initially laging the drug release for 3 hrs and having better sustainability.
- When we plot the release rate kinetics for best formulation f10 was following zero order because correlation coefficient value of zero order is more than first order value.
- F10 formulation diffusion exponent n value is2.081 i.e is n >0.89 so they are following super case II mechanism.
- Higuchi plots F10 formulation is not having good correlation values so the drug is release is not following diffusion mechanism.

CONCLUSION

The aim of the proposed work was to develop pulsatile release tablet of Nebivolol with lag time of 3-4 hrs and fast drug release thereafter. HPMC K15M, Xanthum gum, Ethyl cellulose used as a polymer for a pulsatile drug delivery system of nebivolol. Ethyl cellulose was respectively showed better Pulsatile drug release of Nebivolol when compared to HPMC K15M and 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, content uniformity and *in vitro* drug release. Formulation F10 gave better pulsatile drug release and in comparison to the other formulations.

REFERENCES

[1]. Smolensky MH, Peppas N. Chronobiology, drug delivery and chronotherapeuitcs. Advanced drug delivery Review 2007; 59: 828-51.

[2]. Survase S, Kumar N. Pulsatile drug delivery. Current Scenario Crips. 2007; Vol.8, No. 2:27-33.

[3]. Reguel D. Nebivolol overview 2000; 57:4-18.

[4]. Krogel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cores. International journal of Pharmaceutics 1999; 187:175-84.

[5]. McConville J, Ross AC, Chambers AR. The effect of wet granulation on the erosion behaviour of an HPMC-lactose tablet, used as a rate-controlling component in a pulsatile drug delivery capsule formulation. European journal of Pharmaceutics and Biopharmaceutics 2004; 57:541-49.

[6]. Efentakis M, Koligliati S, Vlachou M. Design and evaluation of dry coated drug delivery system with an impermeable cup, swell able top layer and pulsatile release international Journal of Pharmaceutics 2006, 311:147-56.

[7]. Karavas E, Gerogarakis E, Bikiaris D. Application of PVP.HPMC miscible blends with enhanced mucoadhesive properties in predictable pulsatile chronotherapeutics. European Journal of Pharmaceutics and Biopharmaceutics 2006; 64:115-26.

[8]. Sharma S, Pawar A. Low density multiparticulate system for pulsatile release of Meloxicam. International Journal of Pharmaceutics 2006, 313:150-58.

[9]. Mastiholimath Vs, Danvagi PM, Jaoin SS. Time and pH dependent colon specific, pulsatile delivery of the ophylline for nocturnal asthma international journal of pharmaceutics 2007;328:49-56.

[10]. Badve SS, Sher P. Korde A, Pawar AP. Development of hollow/ porous calcium pectinate beads for floating –pulsatile drug delivery. European Journal of Pharmaceutics and Biopharmaceutics 2007;65:85-93.

[11]. Lin H L, Lin S.Y. Release characteristics and in vitro-in vivo correlation of pulsatile pattern for a pulsatile drug delivery system activated by membrane rupture via osmotic pressure and swelling. European Journal of pharmaceutics and Biopharmaceutics 2008, 70:289-301.

[12]. Li B, Zhu J, Zheng C, Gong W. A novel system for three- pulse drug release based on 'tablets – in-capsule device. International Journal of Pharmaceutics 2008; 352159-64.

[13]. Nayak UY. Shavi GV. Chronotherapeutic drug delivery for early morning surge in blood pressure. A programmable delivery system. Journal of Control Release 2009; 136:125-31.

[14]. Roy P, Shahiwala A. Statistical optimization of ranitidine HC1 floating pulsatile delivery system for chronotherapy of nocturnal acid breakthrough. European Journal of Pharmaceutical Sciences 2009; 37:363-69.