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Formulation and Optimization of Pulsatile Tablet for Circadian Rhythm of Blood Pressure

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Abstract: *Circadian rhythm is a 24-hour cycle of human body, the body different aspect in the morning as compare to afternoon or night. The blood pressure rises in two time in a day, one is at early morning and second one is at evening.The aim of present project work was to design the pulsatile tablet for treatment of blood pressure with combination drug therapy. in most cases it is seen that the increasing in Plasma norepinephrine level and plasma renin activity in the morning; both hormones are potential to induce coronary vasoconstriction, therefore, there is a need to a such formulation who achieve peak plasma concentration of drug at morning and can control morning spate of B.P. The pulsatile release of nebivolol after the lag time with sustain release of curcumin which maintain the severity of blood Pressure. The Formulation of Core tablet of nebivolol was prepared by using super-disintegrate by direct compression with diluent. F10 batch was found to be optimized formulation as it shown potent drug release within short time. The lag time was prolonged with an increase of the coating level, whereas the drug release rate was almost constant, irrespective of the coating level the lag time of nebivolol was found to be 8 to 8.5hrsand drug release after 9hrs. drug release was above 95% after lag time with constant release of curcumin. Hence, this approach can provide a useful means and may be helpful for patients with morning spate of BP and development of PDDS of combination drug therapy is a promising approach to overcome the side effect of single drug i.e. nebivolol drug therapy and also oral drug delivery.*

Keywords*:Pulsatile drug delivery system, Lag time, Circadian rhythm, Non-steroidal anti-inflammatory drug, Super-disintegrate*

I. Introduction

Pulsatile drug delivery system is actually the release of drug with such a manner where drug is released very rapidly after a well-defined lag time or gap of time according to circadian rhythm of the body. These situations therefore compel designing a delayed fast release system.

The delivery of drug is based upon the quantity of drug is released from the dosage form within this lag time is negligible and after that all drug is released in burst manner. Among all the delivery, the oral controlled pulsatile drug delivery system represents the most popular form of controlled drug delivery system for the advantage of oral route of drug administration such system to maintain a plasma concentration of drugs within the therapeutic windows for longer number of pathetical cases such as blood pressure are mostly happening at morning.

Chronobiology is the study of biological rhythms and the mechanisms of biological timekeeping. Chronobiology is delivery systems which are developed to deliver drug respective to the circadian behavior of diseases in the body which are occurring after a specific time interval. The product follows a sigmoidal drug release profile are defined by the time period of no release (lag time) followed by a rapid and complete drug release.

Many Drugs exhibit tolerance which should not be delivered at a constant rate, since the drug effect decreases with constant drug release. In addition, drug toxicity increases rapidly with time when drug concentration is constant. In such cases there is need to option for dosage form which provides desire concentration of drug at required time point only. Theory of chrono pharmaceutics has been emerging, where research is purposed to the development and

evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally fulfill the biological requirement of a given disease treatment.

These systems are designed based on the circadian rhythm of the body. However, there certain condition of drug which such a release pattern is not suitable. These are condition release of drug after lag time. The essential advantages of chrono-therapeutics delivery system have been reported and proved for number of diseases like asthma, arthritis, cancer, diabetes, epilepsy, hypertension, ulcer, hypercholesterolemia etc.

II. Chronobiology of Blood Pressure

Several functions such as, Blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system is concern with circadian rhythms. The capillary resistance and vascular reactivity are high in the morning and later decreasein the day. Blood Platelet aggregability is higher and fibrinolytic activity is lower in the morning, resulting state of relative hypercoagulability of the blood. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events. BP is usually lowest during the sleeping period and further rises sharply in the early morning.

Nebivolol is highly cardio-selective beta-blocker who targets central systolic BP and reduces it magnificently along with extensive hypertension. Nebivolol is a rare $beta_1$-blocker for $beta_1$-adrenergic receptors selectivity than other agents in this class and a nitric oxide (NO) group is present which produces vasodilatory effect which is unique in among all beta-blockers which are currently available in clinicians.

Curcumin control the regulation of AT_1R expression present in vascular smooth muscle cells and found to produce the physiological beneficence of this regulation in angiotensin (Ang) II-induced hypertension. This results into decreasing into AT_1R expression in a concentration- and time-dependent manner in vascular smooth muscle cells

III. Material and Method

***Material*:** Nebivolol (Analab fine chemicals, Mumbai), Curcumin (Otto chemicals, Mumbai), Chitosan (Analab fine chemicals, Mumbai), Cross-povidone (Analab fine chemicals, Mumbai), Sodium starch glycolate (Analab fine chemicals, Mumbai), Mannitol (Analab fine chemicals, Mumbai), Microcrystalline cellulose (Analab fine chemicals, Mumbai), HPMC K100M (Analab fine chemicals, Mumbai), POLYOX WSR-301 (Analab fine chemicals, Mumbai).

Instrument: UV-Spectrophotometer (Shimadzu UV 1700, Japan), FTIR (Shimadzu iris 400), Tablet compression machine (CIP machineries, Pvt. Ltd. Ahmadabad), Kbr press coater (Lab Hosp), Hardness tester (Monsento), Thickness tester (Varnier caliper), Dissolution apparatus (Veego scientific, Mumbai).

III. Preformulation Studies

A. Characterization of Nebivolol:

a) IR Spectra of Nebivolol And Curcumin

IR Spectra of Nebivolol and curcumin was obtained using Shimadzu FT-IR Spectrophotometer, the drug was mixed with KBr and compressed with 5 ton of weight and the solid pallet was kept in light path and obtained spectrum recorded. Thewavelength maxima (λmax) was determined by using UV-Spectroscopy, the Melting point of Nebivolol and curcumin wasdetermined by the capillary method.

b) Determination of λmax

the λmax of both drugs i.e. Nebivolol and Curcumin was calculated by using UV-Spectrophotometer (Shimadzu UV 1700, Japan) Nebivolol and curcumin (10mg) was accurately weighed and dissolved in 100 ml DMSO individually in two 100ml of volumetric flask and final volume was filled upto 100ml. The stock solution (1000µg/ml) was further diluted using distilled water to get serial dilutions (5 to 50 µg/ml). The solution was kept in a fused silica cuvette. The UV spectrum was recorded in the range of 200-600 nm on double beam UV visible spectrophotometer at 1 cm, slit width. The maximum spectrum and wavelength of 285 for nebivolol and 435 for curcumin and were recorded.

c) Drug-Excipient Compatibility Studies:

IR Spectra of Nebivolol, excipient and drug + excipientwas obtained using Shimadzu FT-IRSpectrophotometerand obtained peaks were interpreted. drug and excipient alone ormixture of drug and excipient in KBr and the mixture was placed in the light path and the spectrum wasobtained.

d) DSC Scanning

Five milligram of drug sample was accurately weighed and placed in the hermetic aluminum DSC pan. The pan was sealed with the help of hydraulic press. The sample was heated in DSC furnace for programmed temperature range 50 to 300^{o}C at heating rate of 0.5^{o}C/min. The nitrogen flux rate was set at 20 mL/min. The study was performed using DSCinstrument.

B. Micrometric Properties:

The angle of repose of different formulation mixtureswas determined by the fixed funnel method. The bulk density and tapped density (TBD) weredetermined by using a Tap density apparatus (Electrolab Pvt.Ltd). The Carr's index (%) and the Hausner's ratio were calculated by using formula.

a) Preparation of Core Tablets:

Core tablet of Nebivolol was prepared by the direct compression method. Super-disintegrate like sodium starch glycolate, chitosan, cross povidone was used microcrystalline cellulose, Mannitol were used as diluent, talc (1%) & magnesium stearate (1%) at 1:1 ratio was used as lubricant and 5 mg of Nebivolol as active pharmaceutical ingredient. The composition of different core tablets formulation (given in Table 1) were tableted to 170 mg using tablet compression machine at Dr. D. Y. Patil college of pharmacy, Akurdi.

IV. Formulation Design

Optimization studies for the nebivolol tablet was performed by using Definitive screening design (Design Expert Software Trial version 12.0), 25 runs were generated. Concentration of super disintegrates, concentration of diluent, was selected as independent variables. Disintegration test (Y_1), % Release of drug in 15 min (Y_2), Friability (Y_3), were selected as dependent variables.

Independent variable	Level (-1)	Level (+1)
Concentration. of super-disintegration	2	5
Concentration of diluent	50	150

Table 1: Optimized Design Batches of Nebivolol

BATCH NO	CONC OF SUPER-DISINTERGRANT	CONC OF DILUENT	TYPE OF SD	TYPE OF DILUENT
F1	2	150	CP	MCC
F2	5	150	CP	MAN
F3	4.73	127.4	CT	MAN
F4	2.225	105.5	CP	MAN
F5	2	50	SSG	MAN
F6	2	150	CT	MAN
F7	3.14	50	CT	MCC
F8	5	150	SSG	MCC
F9	3.35	140	SSG	MAN
F10	5	77.5	SSG	MAN
F11	2	112.22	SSG	MAN
F12	2’6	58.5	CT	MAN
F13	4.76	94.5	CP	MCC
F14	2.375	50	CP	MAN
F15	4.73	127.403	CT	MAN
F16	5	50	CT	MCC
F17	4.76	94.5	CP	MCC
F18	5	88	SSG	MCC
F19	2.975	117	CT	MCC
F20	3.65	59.77	SSG	MCC
F21	2	122.5	SSG	MCC
F22	2.975	117	CT	MCC
F23	2.9	150	CP	MCC
F24	3.245	150	CP	MAN
F25	4.1	50	CP	MAN

Table2. Formulation batches of core tablet.

Where- CT- Chitosan, CP-Cross-povidone, SSG- Sodium Starch Glycolate, MCC-Microcrystalline cellulose, MAN-Mannitol

Formulation of Core Tablet by Direct Mixing:

In this method the coating material along with curcumin mixtures were passed through the sieve no.44 and one part of the powder mixture was used for the lower shell and two parts at upper shell. A one part of the powder was filled into lower bed, in the center of which core tablet was placed manually. Then now the remaining two parts of coating material filled in the upper layer of core tablet, and the contents was press under a sufficient compression force, using a suitable punch.

V. Evaluation of pulsatile Tablet

Pre-Compression-Studies

a) Angle of Repose:

The angle of repose of granules was determined by thefunnel method. The granules were poured into funnel and allowed to pass through the funnel freely onto the surface. The diameter and heightproduced by the powder cone was measured and angle of reposewas calculated using the following equation.

$$\mathbf{Tan\ \theta = h/r}$$

The powder which shows range between 25-30 are ideal.

b) Bulk Density:

It is a ratio of weight of powder to bulk volume. The value of bulk density depends on particle size distribution, shape, and cohesiveness of particles. Both lose bulk density (LBD) and taped bulk density(TBD) were determined and calculated by using thefollowing formulas.

LBD = weight of the powder / volume of the powder

TBD = weight of the powder / taped volume of the powder.

c) Compressibility Index:

The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability thecompressibility index of the granules was determinedby Car's compressibility index.

Car's index (%) = [TBD-LBD] /TBD X 100

d) Hausner's Ratio:

Hausner's ratio is actually an indirect index of serenity of powderflow. As such, they are measures of the relative importance of inter particulate interactions. The free-flowing powder exhibit such interactions which is generally significant, and the bulk and tapped densities are closer in value. It is calculated by the following Formula.

Hausner's ratio= Dt/Db

Where, Dt is the taped density,Db is the bulk density

Post Compression Parameters

a) Weight Variation:

All prepared tablets were evaluated for weight variation.In these twenty tablets of each batch were used to evaluate. Weight variation among these 20 tablets was calculated.

b) Friability:

Friability testing was done by Friability test apparatus.The percentage friability was then calculated by,

% Friability = [(W1 – W2) /W1] × 10

% Friability of tablets less than 1% is theoretically acceptable.

c) Hardness:

Hardness of all batches were determined using tablethardness tester (Monsanto hardness tester).

d) Thickness

Thickness was measured by Vernier calipers andreadings were carried out in triplicate and average valuewas noted.

e) In – Vitro Dissolution Studies:

The dissolution testing of pulsatile drug delivery systemwas carried out using a USP Type II paddle apparatus in 900 ml of 0.1 N HCl.The dissolution medium was maintained at 37• }0.5 °Cand the paddle was rotated at 100 rpm. At different timeintervals, 5 ml of sample was withdrawn and analyzed byUV-Visible spectrophotometer at 281 nmat

each timeof withdrawal as 5min, 10 min 15 min, and 5 ml of fresh corresponding medium wasreplaced into the dissolution vessel.

f) Disintegration time

Press coated tablet should give a burst release after predetermined lag time. For this purpose of core tablet must show at least possible disintegration time. The disintegration time of tablet was performed by a disintegration apparatus at 37 ◦C. Six tablets were tested to report the average disintegration time.

Evaluation of Immediate Release Core Tablet

all batches are evaluated with pre-compression and post compression parameter, pre-compression parameter such as angle of repose (ranges between), bulk density, tapped density was found to in limit and they obey all the value limit as in the Indian pharmacopeia, the batch no. 4,7,10,11,12,13,14,16,18 was found to be shows good value of powdered properties. The post compression parameter such as hardness, friability, drug content, disintegration time was also found to be in limit for above batches. In weight variation test, the pharmacopeial limits for the tablets of not more than 10% of the average weight the tablet hardness and friability were found to be around 6 kg/cm2 and below 1%, demonstrating the integrity and strength of tablets. The conc of mannitol and MCC in the formulation affect the tensile strength and powder properties. The more mannitol the weakens the hardness of core tablet, the more mcc weakens the disintegration of tablet.

After evaluation and optimization of every batches, the batch F10 was found to be optimized. The further study and formulation of press coated tablet was formulated as F10 as core tablet. The combination of two polymer chosen as it shows maximum lag time with their maximum viscosity characteristic of their respective polymer.

VI. Formulation Design

Optimization studies for the pulsatile tablet was performed by using Definitive screening design (Design Expert Software Trial version 12.0), 11 runs were generated. Concentration of polymer such as POLYOX WSR-301,HPMCK100M was selected as independent variables. Lag time of pulsatile tablet (Y_1),was selected as dependent variables.

Table 3 Design: Response Surface Optimal Design.

Factor	Level	Level
	-1	+1
POLYOXWSR-301	20	30
HPMC K100M	50	100

Formulation of Press Coated Tablets:

Table 4 Formulation Table of Press Coated Tablets

batch	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11
POLYOX WSR 301	30	23.6	21.5	20	25.7	22.2	25.8	30	30	26.4	20
HPMC K100M	50	100	50	81.5	71.25	67.4	50	92.5	71.5	89	99.7

VII. Evaluation

Pre-Compression Parameter For Press Coated Pulsatile Formulations

Table 5: Pre-Compression Parameter for Press Coated Pulsatile Formulations

Batch	Bulk Density (Gm/Cm^3)	Tap Density (Gm/Cm^3)	Carr's Index	Hausner's Ratio	Angle Of Repose
C1	0.667±0.014	0.909±0.013	16.62±0.12	1.16±0.09	24.07±0.10
C2	0.681±0.016	0.833±0.016	18.24±0.11	1.22±0.013	27.32±0.12
C3	0.714±0.018	0.952±0.019	15.00±0.14	1.13±0.016	31.07±0.14
C4	0.689±0.016	0.833±0.017	17.28±0.15	1.20±0.014	28.40±0.16
C5	0.645±0.013	0.800±0.007	19.37±0.08	1.15±0.011	30.14±0.11
C6	0.740±0.019	0.869±0.011	14.84±0.13	1.17±0.010	26.79±0.18
C7	0.625±0.012	0.769±0.019	18.39±0.16	1.23±0.017	28.51±0.17
C8	0.600±0.09	0.789±0.022	19.95±0.18	1.21±0.015	26..42±0.09
C9	0.769±0.015	0.909±0.017	15.40±0.15	1.18±0.016	27.54±0.11
C10	0.714±0.018	0.952±0.010	13.19±0.16	1.23±0.012	26.49±0.14
C11	0.652±0.017	0.833±0.012	18.72±0.12	1.17±0.014	31.23±0.15

all batches are evaluated with pre-compression and post compression parameter, pre-compression parameter such as C1, C2, C4, C7, C8, C9, C10 bulk density, tapped density was found to in limit and they obey all the value limit as in the Indian pharmacopeia, the batch was found to be shows good value of powdered properties. The values obtained for Angle of repose foe all formulations are tabulated in table no. the values are found to be in the range from 26.74±0.13 to 34.07±0.10. above mentioned batches Showed excellent flowability exhibiting the angle of repose below 30^0C.

Table6: Post-Compression parameter of press coated pulsatile formulation

Batch	**Thickness (mm)**	**Hardness (kg/cm^2)**	**Friability (%)**
C1	3.80±0.06	6.2±0.27	0.705±0.02
C2	3.75±0.03	5.7±0.12	0.609±0.05
C3	3.82±0.07	6.2±0.57	0.681±0.011
C4	3.74±0.033	6.0±0.13	0.598±0.06
C5	3.72±0.05	5.9±0.22	0.611±0.046
C6	3.84±0.07	6.1±0.21	0.678±0.013
C7	3.82±0.06	6.2±0.27	0.684±0.022
C8	3.73±0.04	5.6±0.56	0.555±0.008
C9	3.74±0.049	5.8±0.16	0.590±0.011
C10	3.79±0.05	5.9±0.24	0.601±0.015
C11	3.81±0.063	5.4±0.19	0.515±0.011

The post compression parameter such as hardness, friability, thickness was also found to be in limit for above batches. In weight variation test, the pharmacopeial limits for the tablets of not more than 10% of the average weight the tablet hardness and friability were found to be around 6 kg/cm2 and below 1%, demonstrating the integrity and strength of tablets.

After evaluation and optimization of every batches, the batch C8 was found to be optimized.

In Vitro Release 0f Pulsatile Table

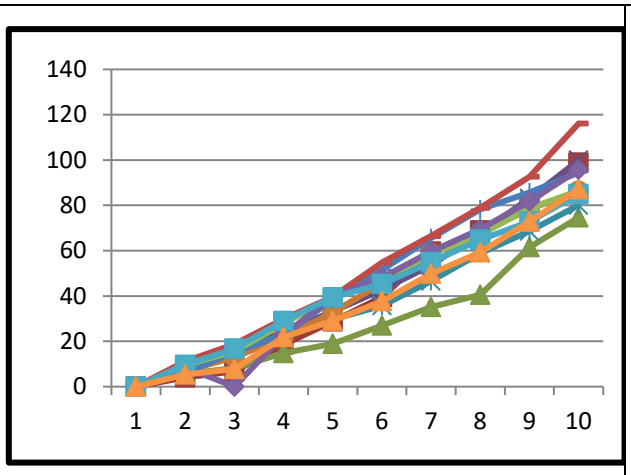

Figure 1: Percentage Drug Release of Curcumin as Controlled Release.

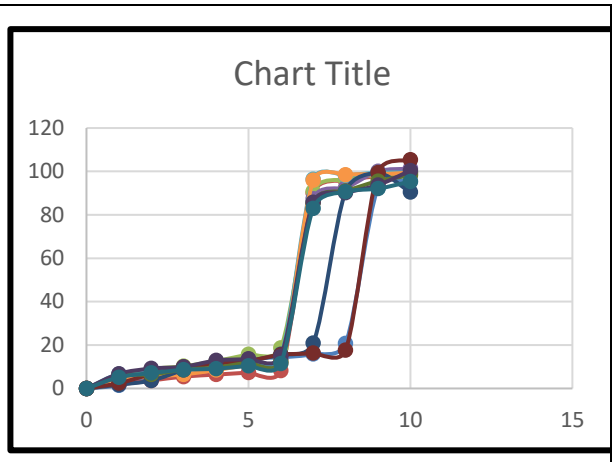

Figure 2: Percentage Drug Release of Nebivolol as Pulsatile Release

VIII. Optimization Study of Immediate Release Core Tablet

ANOVA For 2FI Model
Response 1: Disintegration Time

Source	F-value	P-value	R^2
Model (2FI)	12.35	0.0002	
A-Sodium starch glycolate	1.16	0.0007	0.9453
B-Microcrystalline cellulose	1.92	0.0022	

For the disintegration tablet, the value of correlation (R^2) was found to be 0.9453, indicating good fit of the model. P value for all independent variable was less than 0.5 indicate model terms are significant.

Final Equation in Terms of Coded Factors

Disintegration Time=: (+20.72+3.59A+0.1928B-9.24AB-4.12C-0.388AC+2.51D-0.5062AD-1.97BC+4.31BD.)

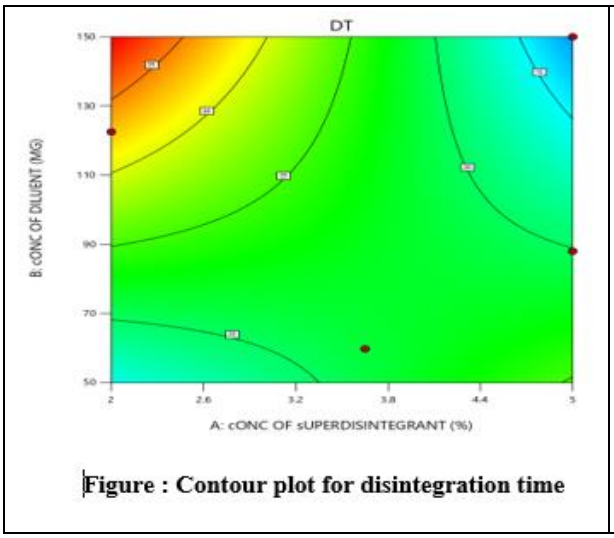

Figure : Contour plot for disintegration time

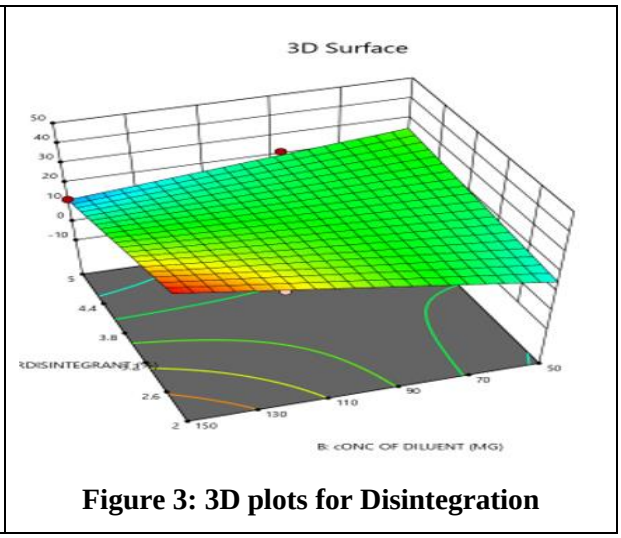

Figure 3: 3D plots for Disintegration

The disintegration time was found in immediate release core tablet of batch F10 is minimum Which is better disintegration time compared to other formulation. When the concentration of Sodium Starch Glycolate and Microcrystalline Cellulose are decreases then disintegration time decreases. While increasing the concentration of sodium starch glycolate and Microcrystalline cellulose then the disintegration time is increases.This may be due to selling of polymer and hydrostatic pressure acting either via swelling or by water wicking or by combination of this mechanism.

Response 2: Dissolution Time

Source	F-value	P-value	R^2
Model (cubic)	15.44	0.0001	
A-Sodium starch glycolate	0.9818	0.0012	0.9598
B-Mannitol	5.48	0.0412	

For the dissolution tablet, the value of correlation (R^2) was found to be 0.9598, indicating good fit of the model. P value for all independent variable was less than 0.5 indicate model terms are significant

Final Equation In Terms of Coded Factors

Dissolution:(+75.39.11.87A-1.64B+0.7424C+1.56D-2.20AB-0.2415AC+0.2613AD-0.4836BC+1.03BD.)

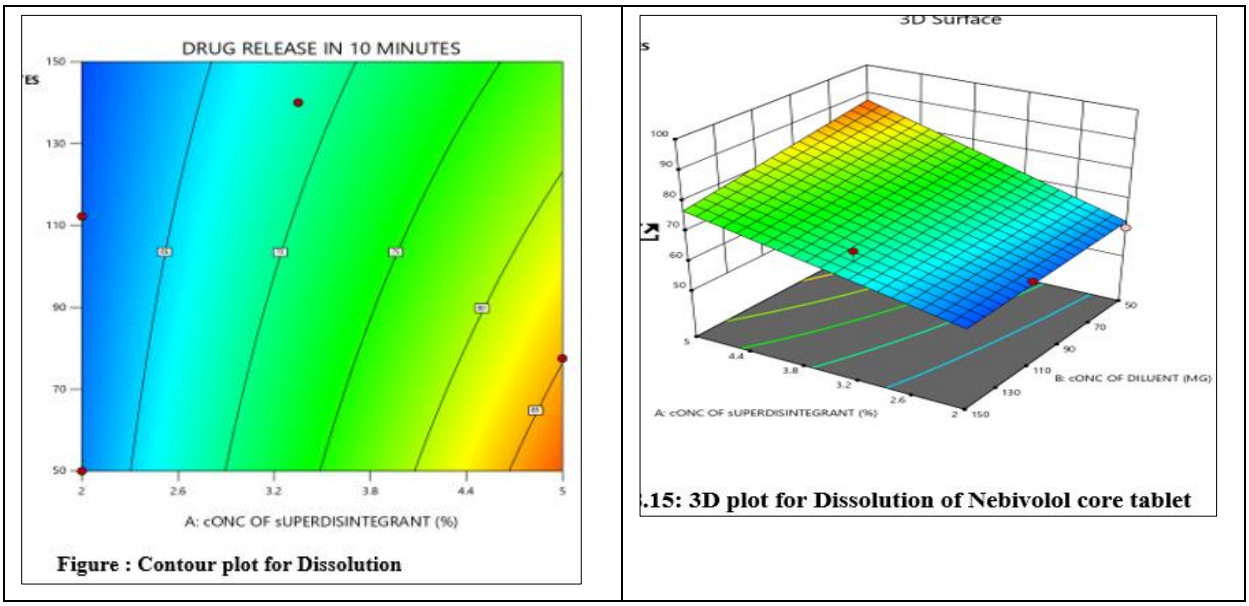

Figure 4: 3D Plot and Counter Plot for Dissolution

The % cumulative drug release of batch 10 was found to be 98% which is better compared to other formulation. When increases the concentration of Sodium Starch glycolate and microcrystalline cellulose then increase the % drug release of core tablet. While decreasing the concentration decrease the % drug release of core tablet. This may be due to selling of polymer and hydrostatic pressure acting either via swelling or by water wicking or by combination of this mechanism. Hence itindicates that the concentration pf polymer in the is directly proportional to the drug release time of tablet and produces an immediate release of tablet

Response 3: Friability

Source	F-value	P-value	R^2
Model (cubic)	35.41	0.0001	0.9802
A-Sodium starch glycolate	37.80	0.0001	
B-Microcrystalline cellulose	0.0458	0.0014	

For the dissolution tablet, the value of correlation (R^2) was found to be 0.9802, indicating good fit of the model. P value for all independent variable was less than 0.5 indicate model terms are significant.

Final Equation In Term Of Actual Factors

Hardness=(+1.34+0.0592a-0.284B-0.146C-0.0197C-0.0808C-0.0086AB0.0249AC-0.0075AD+0.0221BC-0.1432BD+00280C-0.0079C.)

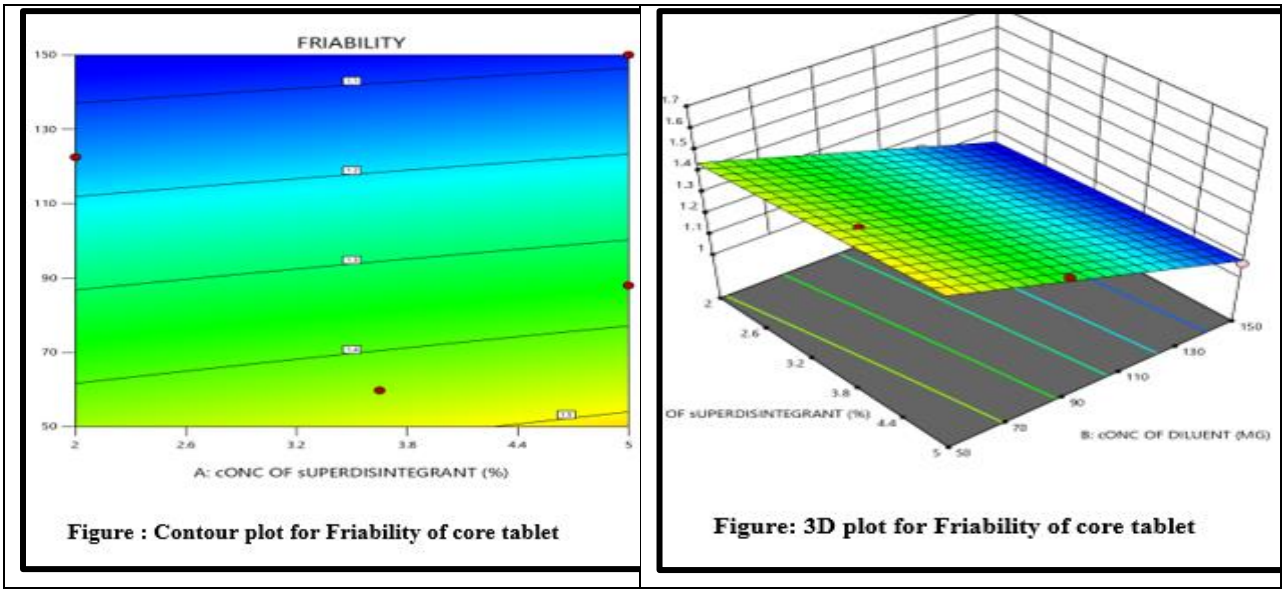

Figure5: 3D Plot and Counter Plot for Dissolution

When increases the concentration of microcrystalline cellulose then increase the friability of core tablet. While decreasing the concentration of and Microcrystalline cellulose then decrease the friability of core tablet. This may be due to tensile strength produced by diluent microcrystalline cellulose to the tablet.

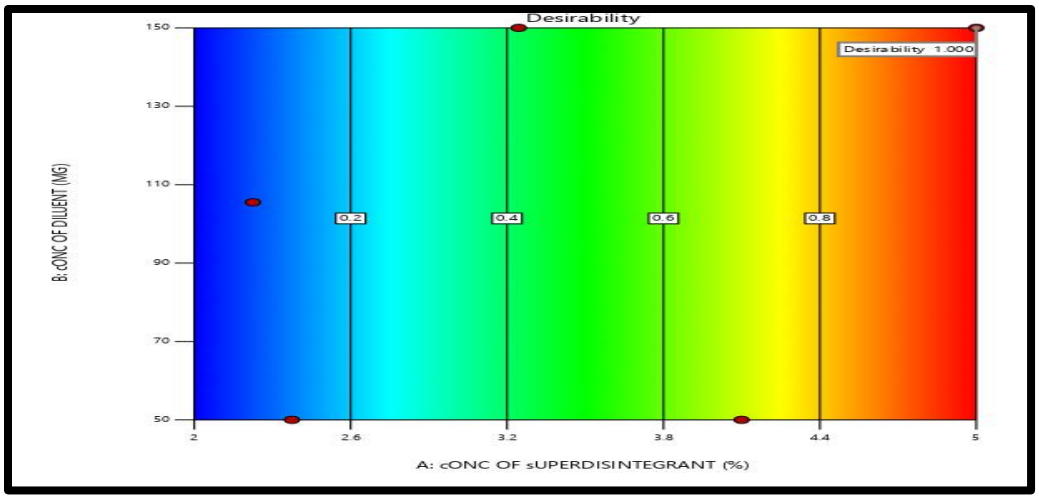

Figure6: desirability plot for core tablet

Design Expert Software criterion of standard being one having the maximum desirability value. The optimization process was performed by setting Y_1 at minimum, Y_2, Y_3, at maximum while all independent variables within range obtained.

The desirability graph of Immediate release tablet shows its desirability at 1.000 which is significant. This desirability graph is obtained as dissolution is key factor, which clearly shows that the drug release increases as the

concentration of polymer increases. The cumulative % drug release profile of batch F10 was found to be optimized formulation as drug release about 98% and disintegration time was found to be 15 sec which was significant, friability was also found in limit. Hence it was concluded that 5 mg of SSG and mg 77.5 of mannitol are produces desired immediate release of tablet. The 3D response surface plot clearly reveals that the concentration of SSG (X1) and amount of Mannitol (X2) affects the release of Nebivolol. Increase in amount of super disintegrate increase the immediate release of tablet. This was observed because the SSG and MCC are easily burst and also increases the tensile strength or friability of tablet while increase in conc of Mannitol increases disintegration time but it reduces the friability and hardness of tablet.

IX. Optimization of Press Coated Tablet

ANOVA for Linear Model
Response 1: lag time Curcumin

Table 7: Lag time of Curcumin

Source	F-value	P-value	R^2
A- POLYOXWSR-301	142.2	0.0017	R^2= 0.9726
B- HPMC K100M	44.46	0.0001	

Final Equation In Term of Actual factor:
Lag time Curcumin= +6.14+1.47A-0.1854B-0.1482A-1.841B

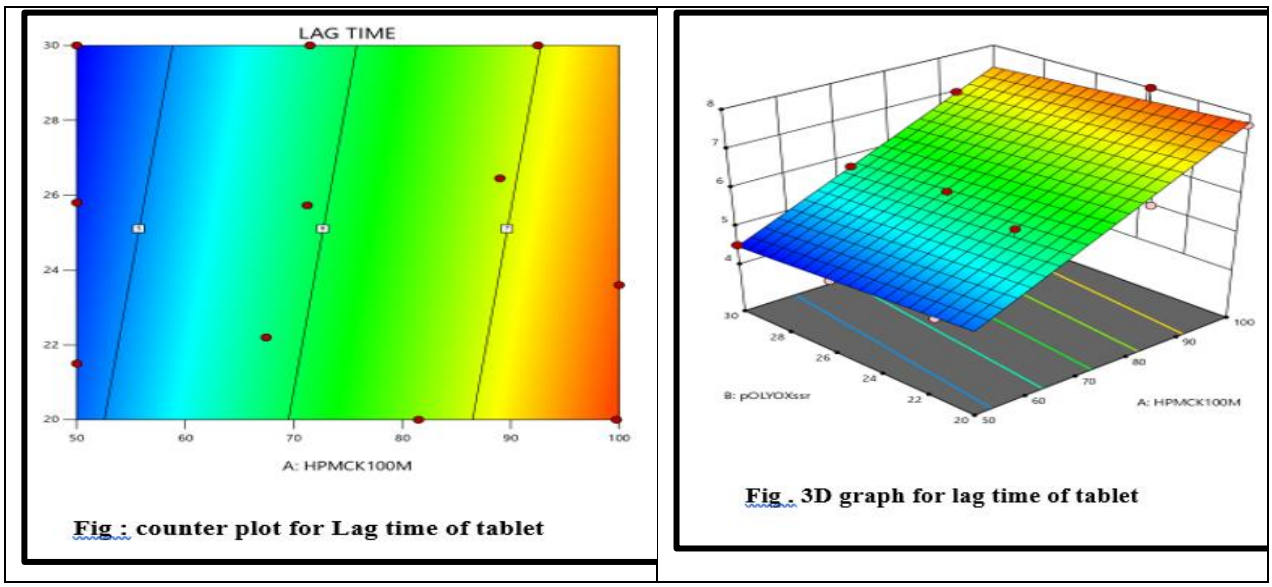

Fig 7. 3D Plot and Counter Plot for Lag Time

From the drug release profile of batch C8 was found to be optimized formulation as shown lag time of Curcumin was 8 to 8.5 hrs and drug release of 17% and 9 hrs drug release was 100% after lag time to be found. Hence it was concluded that polymer i.e. POLYOX WSR-301, HPMCK100M are controlled the desired lag time.

The 3D response surface plot clearly reveals that the concentration of polymer POLYOX WSR-301 (X1) and amount of HPMC K100M (X2) affects the release of Curcumin.

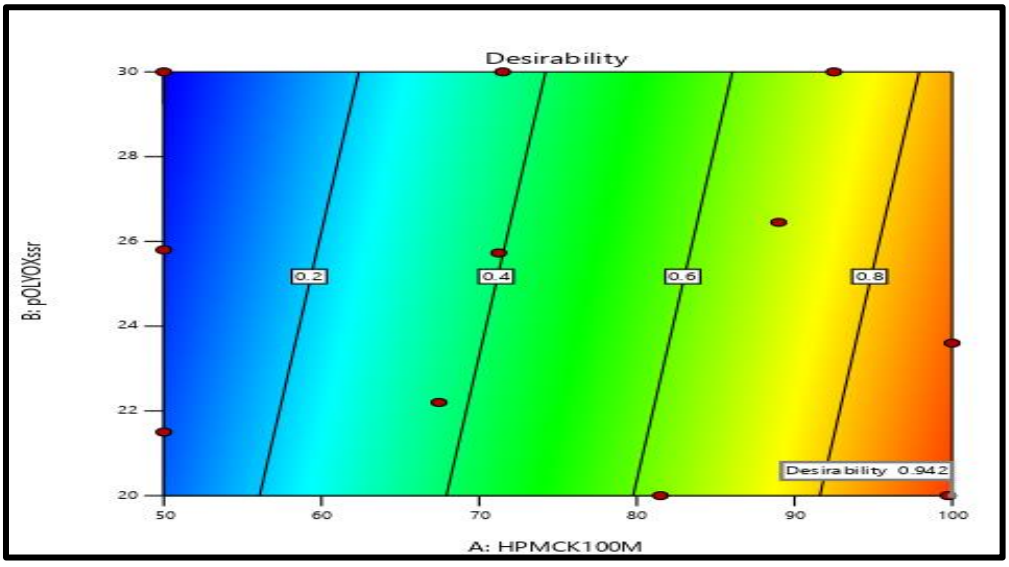

Fig 8 Desirability Graph for Lag Time of Tablet

Design Expert Software criterion of standard being one having the maximum desirability value. The optimization process was performed by setting Y_1, Y_2 at maximum while all independent variables within range obtained.

The desirability graph of lag time of pulsatile tablet shows its desirability at 0.942 which is significant. This desirability graph is obtained as lag time is key factor, which clearly shows that the lag time of tablet increases as the concentration of polymer HPMCK100M and POLYOX WSR-301 increases.

This was observed because the POLYOX WSR-301 and HPMC K100M are easily swell but increases the concentration of HPMC K100M are controlled the lag time. ANOVA table model terms A (POLYOX WSR-301), B (HPMC K100M) and C (HPMC K100M) was found to be significant. A and C are increasing the concentration of polymer are positive sign and B are decreases concentration of polymer are negative sign, which indicate that increasing amount of POLYOX WSR-301 and HPMC K100M cause increasing lag time % drug release. While decreases the concentration of polymer was decrease the lag time and % drug release.

X. Conclusion

Various conclusions can be withdrawn from the present work are follows:

The present study to overcome the oral side effects of Nebivolol and reduce the dose of Nebivolol to overcome the side effects of Nebivolol Curcumin combined therapy. Thus, formulating pulsatile drug delivery system containing Nebivolol and Curcumin in combination for local action against osteoarthritis.

In this study the pulsatile tablet was prepared, which consist of two part, the immediate release core part and other is controlled release coating polymeric part.

Pre-formulation study identification of Nebivolol and curcumin was done and it was found that Nebivolol shows melting point was75^0C and curcumin shows melting point 182^0C and wavelength of maximum Nebivolol 224 and wavelength of maximum curcumin 423 in ethanol, Characterization of FTIR peaks show all functional groups of Nebivolol and curcumin are compatible with the co-excipient and polymer. Core tablets of Nebivolol using super disintegrates were formulated by mentioned in the formulated table. The batch F10 was optimized which contains sodium starch glycolate 5 mg as super disintegrate, because as it shows lower disintegration time and good dissolution profile.

Core tablets were further press coated using various polymers like HPMC K100M POLYOX WSR-301. Among all the 3 batches shows better results and after applying design expert batch C8 was found to optimized. Due to combination of polymers it provided the lag time of about 8 hours which may be due to the properties of the polymers which are gastro-retentive and produce a longer lag time. A drug delivery system with a lag time of around

8 hours with controlled release of curcumin and immediate release of nebivolol, the pulsatile tablet was successfully developed.

Hence, it can be concluded that present study to development of PDDS of combination drug therapy is a promising approach to overcome the side effect of single drug i.e. Nebivolol drug therapy and also oral drug delivery.

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