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Effect of Hydroxypropyl Methylcellulose and Microcrystalline Cellulose in Design and Optimization of Nebivolol Hydrochloride Immediate Release Tablets by Response Surface Methodology

Ramu Samineni*[1], Jithendra Chimakurthy[1], Sathish Kumar Konidala[1], Udayaratna K[2], Devatulasi K[2], Ager Dengoc[2]

[1]Faculty of Pharmacy, Department of Pharmaceutical Sciences, Vignan's Foundation for Science, Technology and Research, India, Vadlamudi, Guntur-522213, Andhra Pradesh, India
[2]Department of Pharmaceutical Sciences, Vignan's Foundation for Sciences, Technology and Research, India, Vadlamudi, Guntur-522213, Andhra Pradesh, India

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ABSTRACT

The goal of the research is to design and optimize Nebivolol Hydrochloride immediate-release tablet using response surface methodology. Nebivolol Hydrochloride immediate-release tablets used in the treatment of heart attacks, myocardial infarction. Response surface methodology calculations for this optimization study were performed utilizing Minitab 17. Different formulations of immediate-release were prepared by applying 2 factors 3 levels full factorial design using Minitab 17, which gave 9 formulations by using the wet granulation method. Independent variables like the amount of hydroxypropyl methylcellulose (X1), and microcrystalline cellulose (X2) and dependent variables like the per cent drug release at 45 minutes (Y1), disintegration (Y2) were selected for optimization. The prepared batches of Nebivolol Hydrochloride immediate-release tablets were evaluated for the pre-compression and post-compression parameters like weight variation, thickness, hardness, and friability, disintegration, and in-vitro drug release studies. All the Physicochemical parameters were found satisfactory for prepared tablets. The optimized formulation F7 showed disintegrated in 83 sec, percentage dissolution release 97.85 at the end of 45^{th} minute. The results shows that formulated immediate-release tablets of Nebivolol HCl were better to meet patient compliance with respect to effectiveness.

*Corresponding Author

Name: Ramu Samineni
Phone: +91 8142853086
Email: samineni.ramu@gmail.com

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INTRODUCTION

Currently, immediate-release tablets have commenced gaining recognition and attractiveness as a drug delivery system, particularly due to the fact they're smooth to administer, have a short onset of action, is inexpensive, and result in better patient compliance. They're also a device for increasing markets, extending product life cycles, and producing opportunities (Sharma *et al.*, 2019; Abhilash *et al.*, 2005; Agarwal *et al.*, 1998).

Nebivolol Hydrochloride is a cardioselective adrenergic beta-1 receptor antagonist (beta-blocker) that functions as a vasodilator through the endothe-

lial l-arginine/ nitric oxide system. It is used to manage hypertension and chronic heart failure in elderly patients. Nebivolol Hydrochloride chemically1-(6-fluoro-3, 4-dihydro-2-H-chromen-2-yl)-2-{[2-(6-fluoro-3,4-dihydro-2H-chromen -2-yl)-2-hydroxyethyl] amino} ethanol hydrochloride represented in Figure 1, (St. Louis, 2007).

The pharmacokinetics of Nebivolol hydrochloride is shown by oral route having peak plasma concentrations approximately in a range of 1.5 to 4 hours, plasma protein binding approximately 98%. Undergoes the first-pass metabolism in the liver mainly via glucuronidation of the parent drug. It is primarily excreted in urine (38%) and feces (44%). Half-life is about 12 hours. Decreased clearance in patients with moderate hepatic impairment or with severe renal impairment. Currently, in the market, this dosage forms available as oral tablets. Stored in a tight, light-resistant container at 20–25° C. (St. Louis, 2007)

The essential intention of the plan is to prepare Nebivolol Hydrochloride immediate-release tablets using semi-synthetic cellulose derivative disintegrants at different concentrations via response surface methodology.

MATERIALS AND METHODS

Nebivolol HCl was procured from Pharma chem Pvt, Ltd. Pregelatinized Starch from Colorcon Asia Pvt Ltd. HPMC E5 and E 15 was obtained as a gift sample from Dow chemical company, microcrystalline cellulose was procured from SD fine chemicals, Mumbai.

Method

Study Type: Response surface methodology, Mini Tab 17, 3 level factorial designs, Quadratic mode (Avachat and Kotwal, 2007).

Response surface methodology (RSM)

It is used for the improvement and optimization of dosage form based on the design of the experiment (DOE) (Ragonese *et al.*, 2002). The technique includes the usage of numerous varieties of experimental designs, mathematical polynomial relationships, and selected responses over the experimental domain to choose the best method (Palamakula *et al.*, 2004; Dayal *et al.*, 2005; Singh *et al.*, 2006, 1995).

Formulation Design of Nebivolol HCl IR Tablets

A software-based response surface methodology approach using 3^2 designs was employed for the optimization study. In the current experimentation, two independent formulation variables were X1: HPMC, X2: MCC and the dependent variables selected were (Y1) % drug release, (Y2) disintegration time. Total 9 different formulations of Nebivolol HCl IR tablets were evaluated to determine the significant effect of selected independent variables on the dependent variable (Basak *et al.*, 2006).

Preparation of tablets by using wet granulation method

Precisely weigh the medication with diluents Lactose monohydrate, PG, Starch and Mannitol pass through 40 no. Sifter and FD and C Blue through 100 sieve number blend it appropriately for 3-5 minutes in a mortar. Prepare the binder solution by dispersing HPMC E5 CPS or E15 CPS and SLS (Sodium Lauryl Sulphate) in purified water. The mixture above is granulated by the prepared binder solution upto the endpoint (dough mass) is obtained. Pass the mass via 30 no sieve and confine a receptacle drier (60-65 ^{0}Cfor 45 mins) for the dried granules. Take the dried granules from the oven and pass to sieve no.30 to get optimum sized granules. Then sifting is done with MCC PH 101 or 102, Polysorbate 80, Aerosil (Colloidal silicon dioxide) through 40 no. sieve, FD and C blue through 100 no. Sieve and Magnesium stearate through 60 no. Sieve. Prelubrication is done by using MCC PH 101 or 102, Polysorbate 80, Aerosil (Colloidal silicon dioxide), and FD and C blue in a polybag. Lubrication is finished by utilizing magnesium stearate recently passed through 40 sieves of the granules for 3-4 min. Croscarmellose sodium is utilized as disintegrate. Compression is finished by using a rotary CADMACH punching machine having 10 station compression machines with round, circular punches of diameter 9.1 mm. Hence, the tablets produced evaluated for an in-vitro test, and the formulation was optimized. Different formulations of tablets by using the wet granulation method represented in Table 1. (Bolton and Bon, 2004; Bourne and Pharmacokinetics, 2002)

EVALUATION OF TABLETS

Organoleptic Properties

The physical identification test like color, odour, taste and appearance of the drug were observed and represented in Table 3.

Determination of Melting point

Melting points of the drug were measured using Gallenkamp (Electronic) melting point apparatus, and reported values are an average of 3 times represented in Table 4.

Determination of solubility

The maximum amount of API placed in 100 ml

of different solvents and measured solubility by using miniaturized shake flask method and reported observation (Bramhanker, 1995; Carmen *et al.*, 2002; Chetoni *et al.*, 1996).

UV-Spectroscopy - Analysis of drug

Required weight 100 mg of the drug is soluble in 100 ml of 0.1N HCl, from that 1 ml pipette out and make up to ten ml, from that 2-12 μg/ml solutions prepared and observed absorbance by using Thermo Scientific UV-Visible spectrophotometer. (Carmen *et al.*, 2002; Chetoni *et al.*, 1996)

Flow property determination

The prepared granules are tested for various Preformulation test based on values flow property were determined. (Carmen *et al.*, 2002; Chetoni *et al.*, 1996)

$$a) Bulk\ density\ (BD) = \frac{Weight\ of\ granules\ taken}{Bulk\ volume}$$

$$b) Tapped\ density\ (TD) = \frac{Weight\ of\ granules\ taken}{Tapped\ volume}$$

$$c)\ Angle\ of\ repose\ \theta = \tan^{-1}(h/r)$$

Where h= height of heap

r = radius of heap

$$d)\ CI = \frac{(T_D - B_D)}{T_D} \times 100$$

$$e)\ HR = TD/BD$$

Uniformity of weight

From the prepared batch, 20 tablets were selected and weighed individually and determined the average weight. Individual weights were compared with the mean weight based on the estimated percentage difference. (Carmen *et al.*, 2002; Chetoni *et al.*, 1996). As per Indian Pharmacopoeia, weight variation limits represented in Table 2.

$$\%Deviation = \frac{Individual\ weight - Average\ weight}{Average\ weight} \times 100$$

Hardness test

It is a pressure required to break a tablet; the crushing power is represented the hardness of a tablet. During handling and transport, the tablet should be stable against mechanical stress. Hardness was tested by means of a Monsanto hardness tester. It calculated and recorded the average of the six determinations. (Carmen *et al.*, 2002; Chetoni *et al.*, 1996)

Friability Test

The variability of the 20 tablets in each batch was tested with a friabilator (ERWEKA, TAR 120, and Germany) at a speed of 25 RPM for 4 minutes. The tablets were subsequently dusted, weighed again, and the weight loss percentage was calculated using the equation below. (Carmen *et al.*, 2002; Chetoni *et al.*, 1996)

$$(W_1 - W_2)/W_1 \times 100$$

Where,

W_1= Initial weight of tablet before friability

W_2= Final weight of tablet after friability

Thickness

Using Vernier callipers, the thickness of the tablets was measured. Recorded the average of the six determinations (Carmen *et al.*, 2002; Chetoni *et al.*, 1996).

Content Uniformity Test

For drug content assessment, 3 tablets per formulation were powdered in a mortar using a pestle; take an amount of powder was equivalent to 10 mg of Nebivolol HCl was transferred into a 100 ml volumetric flask diluted to 100 ml with a sufficient amount of buffer (pH 1.2). The aliquot portion of the filtrate was then appropriately diluted and analyzed by spectrophotometry at 269 nm against a blank. (Carmen *et al.*, 2002; Chetoni *et al.*, 1996)

Disintegration

The disintegration time of the tablet is measured in minutes (or) seconds. In each test tube, one tablet is placed, and the basket rack is positioned in a 1000 ml beaker which consists of distilled water at 37$\pm$0.5° C such that the tablet stays 2.5 cm underneath the surface of liquid on their higher movement and no longer closure than 2.5 cm from the lowest of beaker in their downward movement. Move the basket containing the tablet up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles/min. Recorded the average of the six determinations (Chien, 1990; Colombo *et al.*, 1999).

In-Vitro Dissolution Studies

Dissolution of the tablet were done using the USP-II paddle technique and 900 ml of 0.01N HCl buffers as the dissolution medium for all formulations in triplicate combinations. The medium was allowed to stabilize at 37°c$\pm$0.5°c. Tablet was placed in the

Table 1: Formulations preparation (F1-F9)

Content	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
Nebivolol HCl	21.76	21.76	21.76	21.76	21.76	21.76	21.76	21.76	21.76
Lactose monohydrate	142	142	124	142	125.19	125.19	125.19	125.19	125.19
Pregelatinized starch	-	12	18	24	24	24	24	24	24
Mannitol-60	-	-	-	-	-	24	31.2	31.2	36
Sodium Lauryl Sulphate	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
HPMC E 5 CPS	2.4	2.4	4.8	-	-	4.8	4.8	7.2	4.8
HPMC E 15 CPS	-	-	-	4.8	4.8	-	-	-	-
Distilled Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
MCC PH 101	63.89	51.89	61.49	33.09	-	-	-	-	-
MCC PH 102	-	-	-	-	49.9	25.27	18.25	15.85	13.27
Cross Caramellose Sodium	5	5	5	7.2	7.2	7.2	7.2	7.2	7.2
Polysorbate 80	0.20	0.20	0.20	2.4	2.4	2.4	2.4	2.4	2.4
Brilliant blue FCF	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Colloidal Silicon dioxide	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total Weight*	240	240	240	240	240	240	240	240	240

* mg/Tablet, Q.S- quantity sufficient

Table 2: Weight variation limits (I.P)

Average weight	Per cent difference
<80 mg	±10
> 80 mg <250 mg	±7.5
>250 mg	±5

I.P-Indian Pharmacopeia

Table 3: Physical identification tests

Parameter	Drug
Colour	White to off White colour
Odour	Odourless
Taste	Tasteless
Appearance	Crystalline powder

Table 4: Determination of drug melting point

Reported value	Observed value
221ºC	220-222ºC *

* Results are mean of three times determination.

vessel containing 0.01N HCl buffer at 50 revolutions per minute. A definite time interval of 5 ml of the aliquot of the sample was withdrawn at 10, 20, 30, and 45 mins and filtered (0.45μm). The volume has been replaced by an equal volume of the new dissolution medium. The samples were analysed by spectrophotometry for absorbance at 269 nm using a UV spectrophotometer. (Kuksal *et al.*, 2006; Chien, 1990; Colombo *et al.*, 1999; Samineni *et al.*, 2019)

RESULTS AND DISCUSSION

Organoleptic Properties

The physical identification test like color, odour, taste and appearance of prepared tablets were observed and represented in Table 3.

Determination of melting point

The observed melting points in a range of 220-222ºC are represented in Table 4.

Table 5: Flow PropertiesDetermination

Formula-tion	BD (gm /cc) *	TD (gm/cc) *	HR*	CI (%) *	AR (θ) *	Flow property
F-1	0.286±1.24	0.342±1.21	1.19±0.98	14.5±0.89	28.47±1.12	Good**
F-2	0.326±1.12	0.384±1.23	1.17±0.78	15.1±0.97	30.12±1.22	Good**
F-3	0.290±1.4	0.338±1.34	1.16±0.89	14.2±0.78	26.41±1.34	Good**
F-4	0.301±1.14	0.350±1.24	1.16±0.68	14±0.76	26.96±1.45	Good**
F-5	0.298±1.32	0.347±1.21	1.16±0.92	16.2±0.89	26.85±1.54	Good**
F-6	0.291±1.21	0.331±1.14	1.13±0.89	12±0.91	26.12±1.32	Good**
F-7	0.285±1.25	0.324±1.32	1.13±0.93	12±0.93	25.22±1.26	Excellent***
F-8	0.314±1.32	0.376±1.13	1.18±0.94	16.4±0.95	27.14±1.28	Good**
F-9	0.294±1.24	0.344±1.32	1.17±0.96	14.2±0.98	25.8±1.46	Excellent***

*Results are mean of three times determination
** Angle of repose value 25-30 indicate good as per IP
*** Angle ofrepose value <25 indicates Excellent as per IP

Table 6: Evaluation of Tablets

Formulation	Weight Vari-ation*	Hardness (kg/cm^2)**	Friability (%)	Thickness (mm)***	Content Uniformity (%)	Disintegration (Sec)****
F-1	242	6.7	0.67	3.0	99.41	145
F-2	239	6.6	0.66	2.75	97.68	127
F-3	238	7.1	0.65	2.6	99.5	101
F-4	241	6.9	0.65	2.8	98.19	114
F-5	234	6.5	0.69	2.8	101.1	120
F-6	239	6.4	0.56	2.6	99.28	102
F-7	241	6.8	0.48	3.2	99.8	83
F-8	240	6.3	0.68	2.6	97.16	107
F-9	239	6.8	0.62	2.59	99.6	96

*Results are mean of 20 Tablets determination
**Results are mean of 6 tablets determination
*** Results aremean of 6 tablets determination
**** Results aremean of 6 tablets determination

Table 7: % Cumulative drug release of formulation (F1-F9) at different time points

Formulation	10^{th} min *	20^{th} min *	30^{th} min *	45^{th} min *
F1	56.1	62.3	76	85.7
F2	36.9	60.42	75.98	91.67
F3	38.92	60.42	84.21	93.47
F4	49.8	76.92	89.84	91.28
F5	38.31	47.57	73.02	90.51
F6	55.6	78.8	91.4	95
F7	73.3	85.11	93.85	97.85
F8	54.9	66.49	89.7	93.72
F9	54.77	71.9	85.63	94.75

*Results are mean of 6 tablets determination

Table 8: Comparative drug release studies of F7 with Innovator in 0.01 N HCL buffer

S.NC	Time (min)	Innovator (Bystolic)	Optimized formulation F7 (%)
1	0	0	0
2	10	71.3	73.3
3	20	76	85.11
4	30	86	93.85
5	45	96.2	97.85

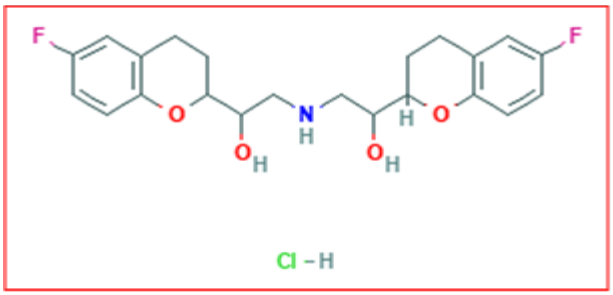

Figure 1: Structure of Nebivolol Hydrochloride

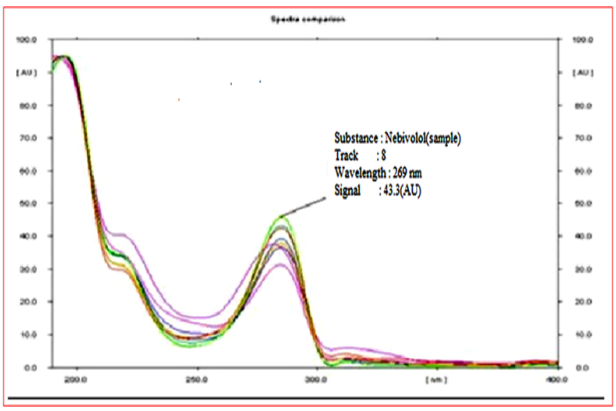

Figure 2: UV spectra of Nebivolol HCl

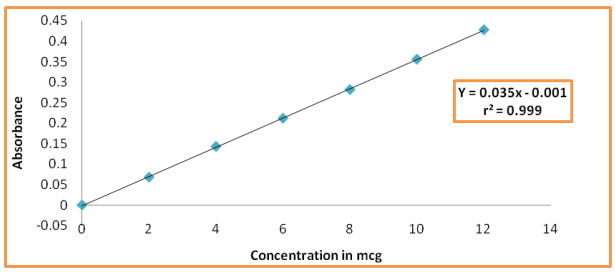

Figure 3: Beer-Lambert's plot for Nebivolol hydrochloride in 0.01N HCl buffer

Determination of solubility

The drug is freely soluble in dimethylsulfoxide, methanol, and N, N-dimethyl-formamide, moderately soluble in propylene glycol, ethanol, and polyethylene glycol, and very poorly soluble in dichloromethane, hexane, and methylbenzene.

UV-Spectroscopy - Analysis of drug

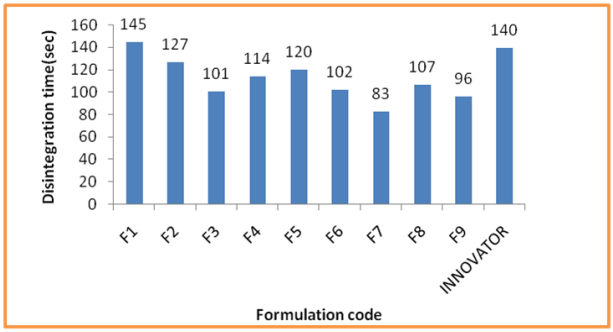

Figure 4: Disintegration time of formulations (F1-F9) and Innovator

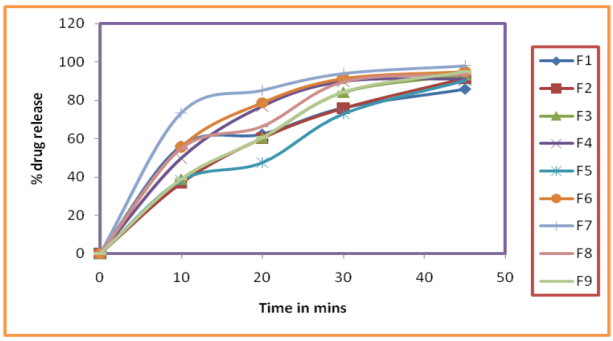

Figure 5: % Cumulative drug released for formulation(F1-F9)

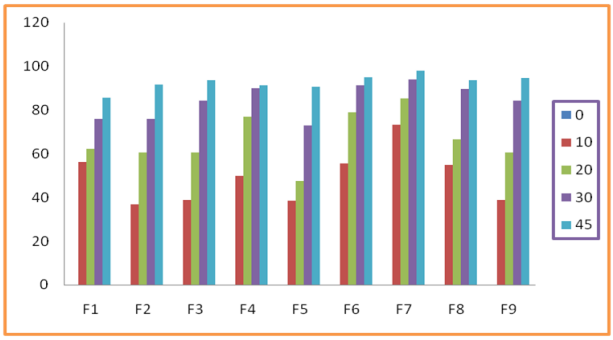

Figure 6: % Cumulative drug released for formulation(F1-F9) comparison at different time points

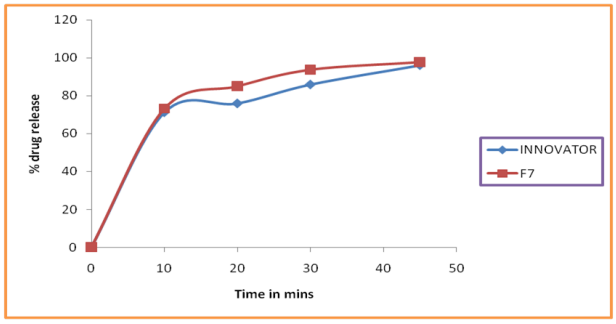

Figure 7: Comparative in-vitro drug release studies of optimized formulation (F7) with Innovator (Bystolic)

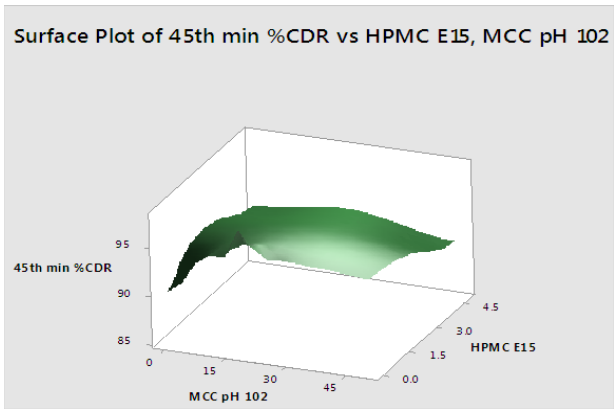

Figure 8: Response surface plot of 45^{th} min % CDR vs. HPMC E15, MCC pH102

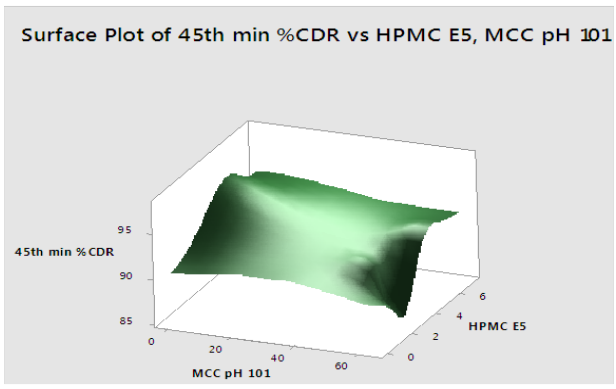

Figure 9: Response surface plot of 45^{th} min %CDR vs. HPMC E5, MCC pH101

The drug sample had a maximum absorption length (λ-max) of 269 nm is represented in Figure 2. Drug shows a linearity range in a concentration range of 2-12μg/ml according to Beer-Lambert's law and represented in Figure 3.

Flow properties determination

The prepared granules for formulation (F1-F9) were estimated, all the formulation values are within acceptable limits and formulations like F7, F9 shows an excellent flow property and remain one show good flow properties represented in Table 5.

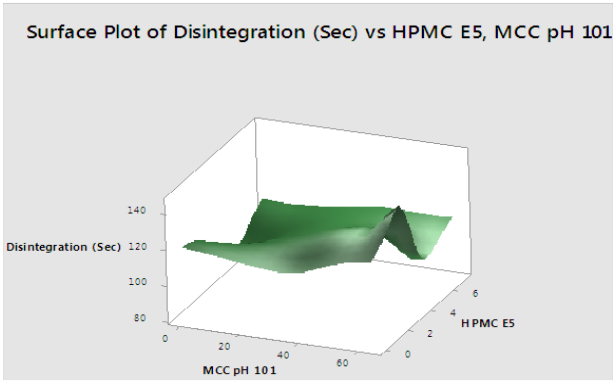

Figure 10: Response surface plot of Disintegration vs. HPMC E5, MCC pH101

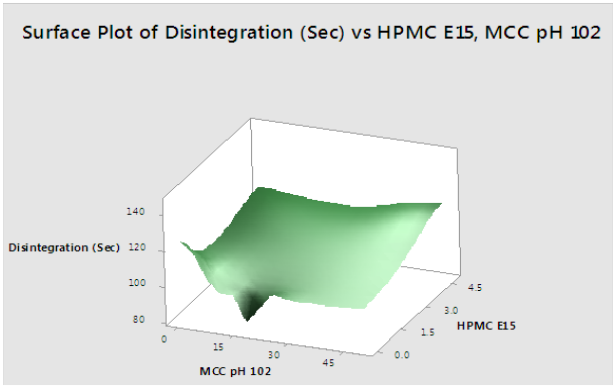

Figure 11: Response surface plot of Disintegration vs. HPMC E15, MCC pH102

Tablet Evaluations

Formulated tablets like F1-F9 were estimated, all the formulation values are within acceptable limits. Weight variation values in a range from 234-242 mg, Hardness values are in a range from 6.3-7.1kg/cm^2, percentage friability of all formulation are less than 1, thickness values are in a range from 2.59-3.2 mm, content uniformity values are in a range from 97.68-101.1%, and disintegration time very less in a formulation F7 compared to other formulations represented in Table 6 and Figure 4.

In –vitro drug dissolution

Optimization

For optimization of a result as suggested by Minitab 17, all the responses were fitted to quadratic and linear models. 3D response surface plots for independent variables effects on % cumulative drug release are represented on Figures 8 and 9 and disintegration time are represented on Figures 10 and 11. The F value for %CDR, disintegration were found to be 3.89, 9.36 respectively, indicating that the models are significant. The values of F were found to be < 0.0001 for all responses indicating that the models are significant. The formulation F7 shows a greater drug release rate 97.85% at the end of the

45^{th} minute compared to other formulations represented in Table 7 and Figure 5. % Cumulative drug released for formulation (F1-F9) comparison at different time points represented in Figure 6. Formulation F7 was selected as an optimized formulation for comparing drug release with innovator product (Bystolic) at different time points represented in Table 8 and Figure 7.

CONCLUSIONS

The prepared formulations shows excellent flow properties, and post-compression parameter values are within standard limits. The formulation (F7) containing HPMC E 5 CPS (4.8 mg), MCC PH 102 (18.25 mg) was showing high drug release (97.85%) compared to all formulations; this formulation was selected as optimized. The results indicated that the formulated immediate-release Nebivolol HCl tablets were effective and better suited to patients.

Hence based on the formulation development and their results, the wet granulation method is more suitable for Nebivolol HCl immediate-release tablets in terms of palatability, physical and chemical properties better with a reference product.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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